UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF MASSACHUSETTS

JOHN HANCOCK LIFE INSURANCE COMPANY, JOHN HANCOCK VARIABLE LIFE INSURANCE COMPANY and MANULIFE INSURANCE COMPANY, Plaintiffs, v. ABBOTT LABORATORIES, Defendant.	CIVIL ACTION NO. 05-11150-DPW

AFFIDAVIT OF PHILIP M. DEEMER

I, Philip M. Deemer, hereby declare and say:

1. My name is Philip M. Deemer. I am over 18 years of age, and suffer from no condition or disability that would impair my ability to give sworn testimony. This affidavit is based upon my own personal knowledge.

Education and Professional Background

2. I am currently employed by Abbott Laboratories ("Abbott") as Director of Alliance Management in the Pharmaceutical Products Division. My supervisor is Richard Marshak, General Manager of Alliance Management.

3. I received a Bachelor's Degree in chemical engineering from the University of Michigan in 1978. I received a Master's Degree in Business Administration from the Carnegie Mellon School of Business in 1982.

4. I began work at Abbott Laboratories in 1990. From 1990 to 1994, I was Manager of Business Development for Abbott's Hospital Products Division. In that position, I was primarily responsible for "in-licensing", *i.e.*, negotiating licenses that

provide Abbott with rights to technology and products owned by other companies. From 1994 until about 2000, I worked in Corporate Licensing for Abbott's Pharmaceutical Division, first as Senior Manager and then as Director of Licensing. In those positions, I was primarily responsible for in-licensing technology and products for the Pharmaceutical Division.

5. From approximately early 2000 until near the end of 2001, I was Director of Business Development and Licensing for Abbott's Global Pharmaceutical Research Division. In that position, my responsibilities included in-licensing, out-licensing (*i.e.*, negotiating licensees for other companies to use Abbott technologies or products), and general business development. During that period, I reported to Ake Johannson, Vice President of Business Development and Licensing. During most of my tenure in that position, Mr. Johannson reported to Jim Tyree, Senior Vice President of Business Development and Licensing, who in turn reported to Dr. Jeffrey Leiden.

6. Near the end of 2001, I moved back to Abbott's Hospital Products Division as Director of Business Development and Licensing. I held that position until approximately January 2004. At that point, I became Director of Global Strategic Operations in the Renal Care Franchise, where I was responsible for evaluating new business opportunities and forming management alliances with other biotechnology and pharmaceutical companies.

Negotiation of the Research Funding Agreement

7. Along with Stephen Cohen, who was then Controller for Abbott's Global Pharmaceutical Research and Development Division, I was responsible for negotiations with Hancock of the business terms of the Research Funding Agreement between Abbott and Hancock (the "Agreement"). Mr. Cohen retired from Abbott shortly before the

Research Funding Agreement was executed on March 13, 2001. Abbott in-house counsel, Daphne Pals and Brian Smith, also participated in the drafting of the Agreement on behalf of Abbott.

8. My counterpart at Hancock in negotiation of the Agreement was Stephen Blewitt, who was principally responsible for negotiating the business terms of the Agreement on behalf of Hancock. Brewster Lee, Kevin Tormey, and Amy Weed, outside counsel at the law firm of Choate, Hall & Stewart, participated in the drafting of the Agreement on behalf of Hancock.

9. In the late 1990s, I negotiated deals which involved collaborative investments by John Hancock and Abbott in the research and development of pharmaceutical compounds by other companies. My counterpart from John Hancock on those deals was Stephen Blewitt.

10. Starting in 1999, Mr. Blewitt and I discussed the possibility of Hancock making additional investments in opportunities being pursued by Abbott. Mr. Blewitt explained that Hancock wanted to make additional investments in the research and development of compounds in which Abbott was also investing. In early 2000, that general concept evolved into the more specific concept of Hancock investing in a portfolio of Abbott compounds in exchange for the right to potential future milestones and royalty payments from any successful commercialization of the compounds.

11. During negotiation of the Agreement, I was aware that Hancock was conducting its own due diligence. For example, I knew Hancock had retained a scientific consultant to research the compounds and the market. I informed Mr. Blewitt that Abbott was open to Hancock doing whatever degree of due diligence was necessary to

familiarize itself with the compounds in the portfolio. At Hancock's request, I set up telephone calls between Abbott scientists and Hancock personnel to answer questions regarding the compounds in the proposed portfolio. I never declined any request by Hancock for additional information regarding the compounds.

Temporary Slow Down of ABT-518

12. During negotiation of the Agreement, I had limited information regarding research and development of the compounds because I worked in business development, rather than in research and development. I generally did not attend portfolio review meetings and did not attend the March 7-9, 2001 Portfolio Review meeting.

13. In early March 2001, as we were finalizing the Agreement, I heard that development of ABT-518 was being slowed down. I telephoned Dr. John Leonard to discuss this issue. Because I believed that the slow down might be related to budgetary constraints, I reminded him that additional funding for development of ABT-518 would be available from the Hancock agreement. I did not have any further conversation with Mr. Leonard about this issue.

14. At some point after my conversation with Dr. Leonard, and prior to execution of the Agreement on March 13, 2001, I was informed that development of ABT-518 would not be slowed down. I was informed that the clinical trial of ABT-518 would continue as planned, that ABT-518 would remain a fully funded program, and that, more generally, ABT-518 development would continue on its normal development timeline. I am not certain who provided this information to me, but I believe it was Stephen Cohen.

15. On March 20, 2001, a week after the Agreement was executed, I wrote an email to Dr. Nisen noting that the Agreement had been consummated. Attached as P's

Ex. AF is a true and correct copy of a March 22, 2001 email string between me and Dr. Nisen, including my March 20, 2001 email. I sent the email because I knew Dr. Nisen believed strongly in the merits of ABT-518 and the other oncology compounds in the portfolio, and would be pleased that additional funding would be available to support development of the compounds. I noted in my email that there was "a little scare at the end when it looked like 518 was being slowed down, which could have been the deathknell to the deal." By that comment, I meant that if ABT-518 was being significantly slowed down, it might have delayed finalization of the agreement and might have required substitution of another compound or other changes to the deal. Based on prior experience, however, I believe that even if ABT-518 had been slowed down, it would not ultimately have prevented finalization of a deal. For example, in Fall 2000, I notified Mr. Blewitt that Abbott was terminating development of ABT-980, an advanced Phase III compound that was then part of the proposed portfolio. After substitution of two earlier stage compounds for ABT-980 and renegotiation of certain terms, we proceeded to finalize the deal. ABT-518 was a very early minor stage compound and much less important financially than later stage compounds, so any impact of a slow down of ABT-518 would have been much less significant than the impact of ABT-980.

16. In any event, at the time I wrote my email to Dr. Nisen, the issue of how a slow down of ABT-518 could have impacted the Agreement was hypothetical, because, as I noted in the email, I understood that ABT-518 was "back on track." Dr. Nisen responded to my email by saying he knew about the 518 "debacle" and said he would tell me more later. Because of his sister's illness and our travel schedules, which are referenced in the emails, I never had an opportunity to talk to him about the issue, but I

understood his reference to the "debacle" to relate to the original slow down of ABT-518, which was a moot issue at the time of the email.

Termination of ABT-518 in Summer 2001 & Notification of Hancock

17. In the Summer 2001, I learned that management decided to terminate internal development of ABT-518. I was informed, however, that patients in the clinical trial were continuing to be dosed and that Dr. Nisen was attempting to get the program funded again. Attached hereto as P's Ex. MU is a true and correct copy of an email I wrote to my supervisor, Mr. Johannson, on August 27, 2001 attaching a weekly update regarding my priority projects. As I noted on page four of the update, I was beginning to prepare to out-license ABT-518 "unless Perry [Nisen] can get it funded again." In the Fall 2001, I was informed that the last patient discontinued enrollment in the trial and that Dr. Nisen had not been able to obtain funding for continuation of the program. Therefore, I attempted to set up a meeting with Mr. Blewitt to inform him in person of the termination of ABT-518 and introduce him to Thomas Lyons, the new R&D Controller (who was replacing Stephen Cohen and would be the point person with Hancock regarding performance of the Agreement). Due to scheduling problems, that meeting had not occurred by September 20, 2001, so Daphne Pals sent a letter to Mr. Blewitt informing him that Abbott had ceased development of the termination of ABT-518. A true and correct copy of that letter is attached hereto as P's Ex. 13.

Attempts to Out-license of ABT-518

18. After ABT-518 was terminated, I led the initial efforts to out-license the compound. Initially, I contacted Alan Rosenthal, the President and Chief Scientific Officer of Salmedix, a biopharmaceutical company based in San Diego, because I

believed Salmedix was a promising prospect for out-licensing of ABT-518. Mr. Rosenthal was tentatively interested and referred me to Wendy Johnson, the Senior Vice President of Corporate Development at Salmedix. Attached as D's Ex. EF is a true and correct copy of an August 22, 2001 email from me to Ms. Johnson, attaching a draft Confidential Disclosure Agreement ("CDA"), along with a set of slides regarding Salmedix that I received from Ms. Johnson. As noted on pages ABBT246356-58 of the slides, Salmedix is a biopharmaceutical company that focuses on developing and commercializing mechanism-based cancer therapies and whose strategy includes in-licensing and developing clinical stage drugs from third parties.

19. Attached hereto as D's EG is a true and correct copy of a September 28, 2001 email from me, along with my weekly update to Mr. Johansson. As reflected on page 3 of the update, by September 28, 2001, Abbott and Salmedix had entered into a CDA and I had sent Salmedix confidential information regarding ABT-518 for their review.

20. After Salmedix received the confidential information, members of the ABT-518 team, including Steven Davidsen, a researcher, and Dr. Nisen, provided information to Salmedix regarding the compound as part of Salmedix's due diligence. Attached hereto as D's Ex. EI is an email from Alan Rosenthal to Mr. Davidsen and Dr. Nisen.

21. I also contacted numerous other pharmaceutical companies in the Fall 2001 to propose potential out-licensing of ABT-518. Companies that I contacted at that time included Amgen, Boehringer Ingelheim, Celtech, Eli Lilly, Genentech, Merck, Pharmacia & Upjohn, Pfizer, Pozen, and Sanofi. For example, attached hereto as D's Ex.

EH is an email that I wrote to Merck on October 12, 2001 regarding out-licensing of ABT-518. Those companies, however, declined interest in licensing ABT-518.

22. Around the end of 2001, I moved to a different position that did not involve responsibility for out-licensing pharmaceutical compounds. At the time I left my position, I had been unable, despite my best efforts, to out-license ABT-518.

23. Attached hereto as D's Ex. EL, EM, EN, EO, EP, EQ, ER, ES, ET, and EU are copies of emails, presentations, memoranda, and reports from Abbott's files. Based on my experience working on licensing and business development at Abbott and my experience working with the authors of these documents, I believe that these exhibits would have been prepared at or near the time of the matter recorded therein by people at Abbott having knowledge of the facts recorded, and that the exhibits would have been kept in the normal course of Abbott's regularly conducted business activities consistent with Abbott's regular practices.

I declare under penalty of perjury under the laws of the United States of America that the foregoing is true and correct and that this affidavit is executed on this 11th day of March, 2008 at Abbott Park, Illinois.

Philip M. Deemer

CERTIFICATE OF SERVICE

I hereby certify that this document(s) filed through the ECF system will be sent electronically to the registered participants as identified on the Notice of Electronic Filing (NEF) and paper copies will be sent to those indicated as non registered participants on March 11, 2008.

Date: March 11, 2008.

/s/ Eric J. Lorenzini

4624339.2

D's Ex EF
Part 1

Philip M Deemer/LAKE/CORP/ABBOTT
08/22/2001 01:58 PM

To "Wendy.Johnson" <WJohnson@salmedix.com>
cc
bcc
Subject Re: Outlicensing Opportunities

Wendy, attached is the CDA for ABT 518. As I mentioned to Alan, we are not sure that we will be able to partner this but in the event we are able to do so, the CDA will allow us to proceed quickly.

Phil

CDo Salmedix DEEMER.do

"Wendy.Johnson" <WJohnson@salmedix.com>

"Wendy.Johnson" <WJohnson@salmedix.com>
08/13/01 04:26 PM

To: <phil.deemer@abbott.com>
cc: "Alan.Rosenthal" <ARosenthal@salmedix.com>
Subject: Outlicensing Opportunities

Dear Phil:

I spoke with Alan Rosenthal this afternoon and he suggested that I contact you directly. I know you have had some conversations with Alan regarding possible drug development opportunities and I can't tell you how pleased we would be to enter into serious discussions with Abbott. It is quite impressive how rich your pipeline has become. Frankly, I never thought of Abbott as an oncology company in the past.

We are looking for an opportunity to continue the development of a clinical candidate for a company that has too much to currently handle- not because the compound doesn't make the cut. Of course from our perspective a straight license would be preferable, however, recognizing that it can be difficult to let something loose, we can discuss a creative deal that potentially could provide opt-in rights.

That being said, to have an opportunity for Alan and I to at least discuss potential opportunities with you would be terrific. Perhaps we can take advantage of the fact that Alan is still commuting back and forth to plan a visit.

I know that you would like to receive a corporate brochure. Unfortunately we don't have one- having been so busy getting the company established and our clinical trial started. It will be put together in the coming months. In the meantime, I have enclosed a short presentation that will give you some perspective of who we are and what we are doing.

I understand that you will forward a CDA as a first step. Looking

forward to receipt and getting to know you.

Sincerely,

Wendy
<<Introductory Slides 8-14-01.ppt>>
Wendy Johnson
Senior Vice President, Corporate Development
Salmedix, Inc.
4330 La Jolla Village Drive, Suite 250
San Diego, CA 92122
858-622-5056 (phone)
858-622-5060 (fax)
wjohnson@salmedix.com

 - Introductory Slides 8-14-01.ppt

D's Ex EF Part 2


salmedix
Salmedix, Inc.
4330 La Jolla Village Drive
San Diego, CA 92122
858-622-5050

Salmedix Mission

- Develop and commercialize mechanism-based, non-DNA damaging, cancer therapies.
- Become a leading biopharmaceutical company focused in oncology, geriatric medicine, and immune diseases by building on scientific and clinical strengths.

Salmedix

Salmedix Strategy

- Focus on cancers with increasing incidence:
  - **B cell malignancies (chronic lymphocytic leukemia, myeloma and lymphomas).**
  - **Prostate cancer.**
- Exploit proprietary discoveries to develop novel, non-cytotoxic drugs.
- Focus internal resources to support clinical-stage drug development.

Salmedix

D's Ex EF Part 3

Salmedix Strategy

- In-license and develop clinical stage drugs from third parties to complement *Salmedix* portfolio.
- Form alliances to support earlier stage programs in angiogenesis, cell signaling and for non-oncology indications

Salmedix

Current Portfolio

	Drugs	Cancer Targets
1. Clinical Stage	SDX-101	• CLL • MM, NHL, prostate
	SDX-102	Leukemias and solid tumors
2. Advanced Pre-Clinical Pipeline	SDX-103	• Vascularized Tumors • CLL
	Small molecules signaling antagonists	• Leukemias and Lymphomas
3. Earlier Pre-Clinical Pipeline	Biological signaling antagonists	Leukemias and other tumors

Salmedix

D's Ex EF Part 4

Key Personnel

Name	Role	Background
Dennis Carson, M.D.	Chair, SAB Board member	Professor of Medicine and Director, Institute for Research on Aging, UCSD Developer of Leustatin Founder of Vical, Triangle and Dynavax
David Kabakoff, Ph.D.	Chairman and Chief Executive Officer	President, Dura Technologies CEO, Spiros Development Corp. I and II CEO, Corvas International, Inc. Sr. VP/VP R&D, Hybritech, Inc.

Salmedix

Key Personnel

Name	Role	Background
Alan Rosenthal, M.D.	President/Chief Scientific Officer Board member	• Sr. VP Scientific Affairs, Abbott Labs • VP Pharmaceutical R&D, Boehringer Ingelheim • VP Immunology, Merck
Wendy Johnson, M.S., M.B.A.	Sr. Vice President, Corp. Development	• VP Business Development, Women First HealthCare, Prizm and Cytel • Assoc. Director, FDA
Anita Busquets	Chief Financial & Administrative Officer	• President, GeneTex, Inc. • COO, CTRC Research Foundation • Director, F&A Corvas International

Salmedix

D's Ex EF
Part 5

Key Personnel

Name	Role	Background
Lorenzo Leoni, Ph.D.	Director, Research	Assistant Professor of Medicine, UCSD Biochemical Pharmacologist
Francis Nardella, M.D.	Medical Consultant	Discovered use of SDX-101 in leukemia Rheumatologist in private practice
Carlos Carrera, M.D.	Clinical Consultant	Associate Professor of Medicine UCSD Co-developer of Leustatin
Pauliana Hall, M.S.	Regulatory Consultant	VP Regulatory Affairs, Sepracor, Inc. Director, Regulatory, Astra Pharmacology R&D, Wyeth-Ayerst

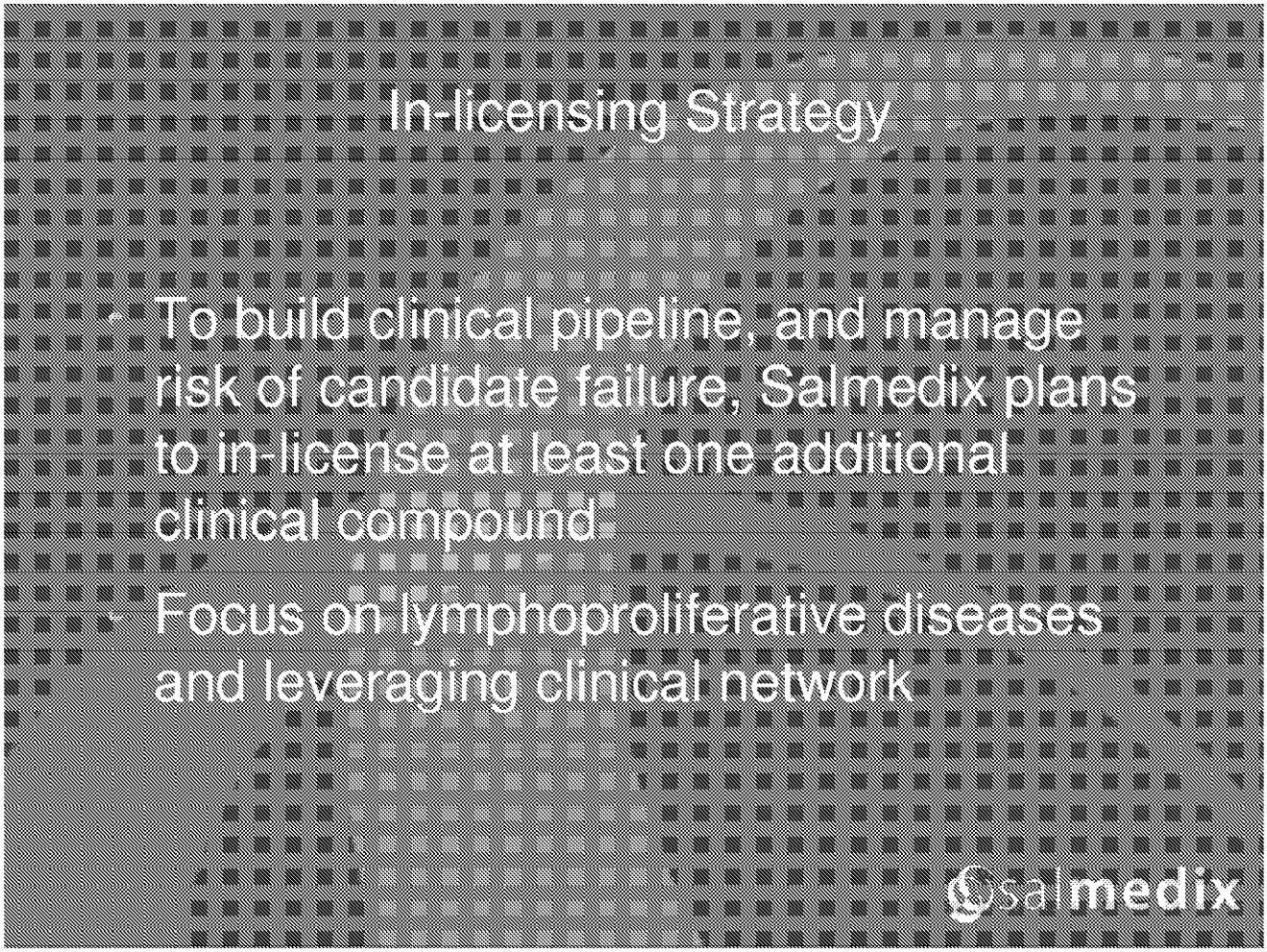
Salmedix

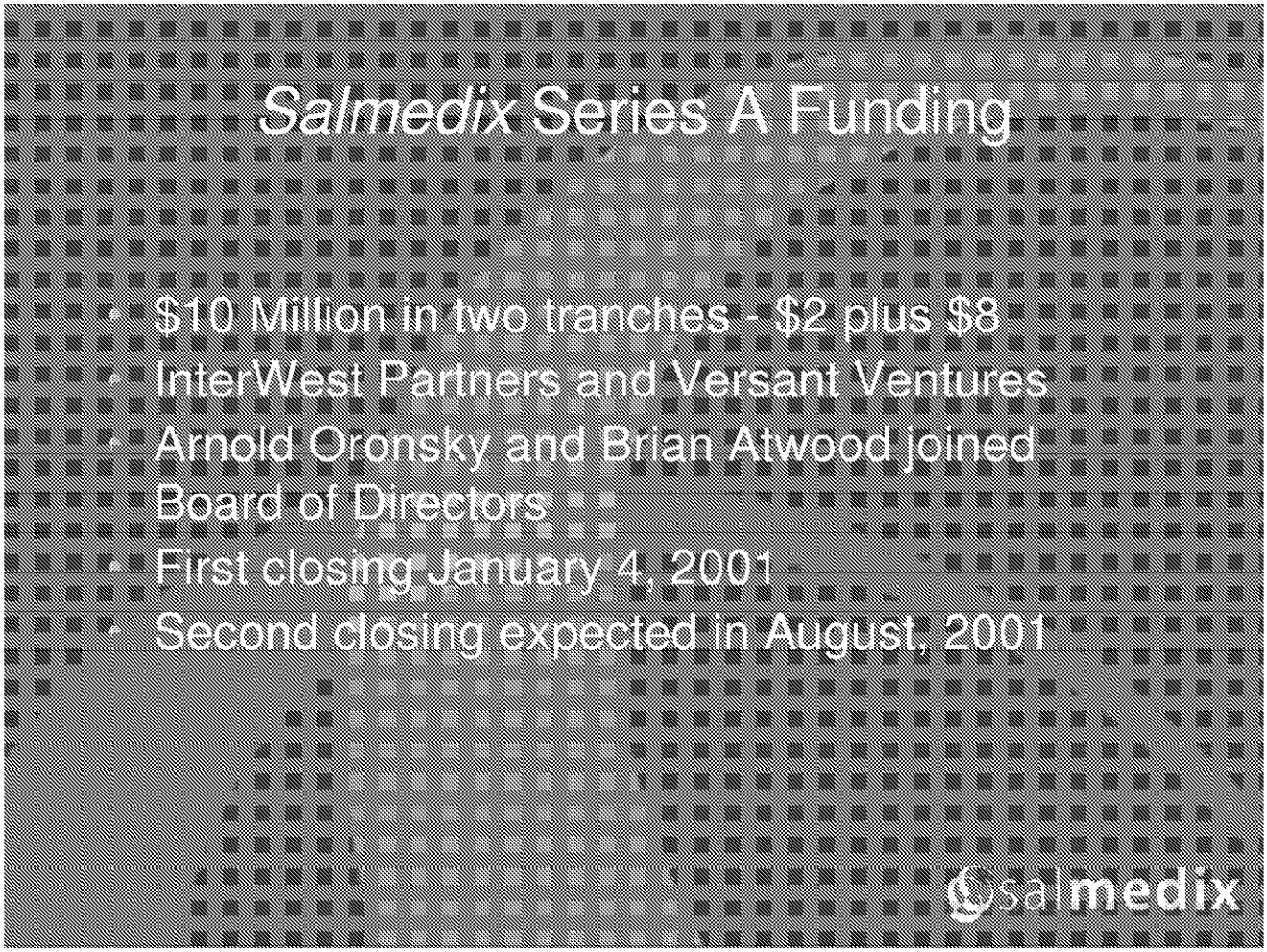
Clinical Advisory Board

- Antonio, Grillo-Lopez, M.D., Chairman
  - *Former Chief Medical Officer, Idec Pharmaceuticals*
- Thomas Kipps, M.D.
  - *Chairman, Dept. of Hematology/Oncology*
  - *University of California San Diego*
- Discussions underway with additional thought leaders

Salmedix

D's Ex EF Part 6


In-licensing Strategy
To build clinical pipeline, and manage risk of candidate failure, Salmedix plans to in-license at least one additional clinical compound.
Focus on lymphoproliferative diseases and leveraging clinical network
Salmedix


Salmedix Series A Funding
• $10 Million in two tranches - $2 plus $8
• InterWest Partners and Versant Ventures
• Arnold Oronsky and Brian Atwood joined Board of Directors
• First closing January 4, 2001
• Second closing expected in August, 2001
Salmedix

Summary

- Track record in cancer, immunology, and geriatric medicine
- Two products in clinical trials
- Short pathway to new drug approval in hematological malignancies
- Lead compounds with demonstrated in vivo inhibition of angiogenesis and cell signaling
- Established scientific and clinical collaborative network

Salmedix

D's Ex EF Part 7

Global Pharmaceutical Research & Development
Abbott Laboratories
100 Abbott Park Road
Abbott Park, Illinois 60064-6050 USA

August 17, 2001

DRAFT FOR DISCUSSION PURPOSES

Ms. Wendy Johnson
Senior Vice President
Corporate Development
Salmedix, Inc.
4330 LaJolla Village Drive
San Diego, California 92122

Ladies and Gentlemen:

This letter "Agreement" will confirm the interest of Salmedix, Inc. ("Salmedix") in obtaining certain proprietary information from Abbott Laboratories ("Abbott"), which Abbott owns and can disclose for purposes hereunder, relating to Abbott's ABT-518 cancer compound ("Compound"), possibly including but not necessarily limited to, chemical, toxicological, preclinical and clinical information regarding the Compound. Salmedix desires to receive and evaluate that information for the sole purpose of determining whether it is interested in pursuing a possible commercial "Arrangement" with Abbott. Abbott will disclose such information on the following terms and conditions:

1. Promptly following the full execution of this Agreement, Abbott shall disclose to Salmedix information in oral, written, visual and/or other form which may include, but not necessarily be limited to, specifications, data, samples, substances and other materials relating to Abbott's Compound ("Information").

2. Salmedix shall promptly evaluate the Information and advise Abbott of its interest, or lack thereof, in an Arrangement. If Salmedix is not interested in an Arrangement, or upon the request of Abbott, Salmedix shall return all Information to Abbott within thirty (30) days of Abbott's request, subject to retention of one (1) complete copy thereof by Salmedix solely for archival purposes to monitor compliance with this Agreement.

3. For a period of Five (5) years following the full execution of this Agreement, Salmedix shall exercise all reasonable care to prevent the unauthorized disclosure of Confidential Information to any third party, and shall not use or allow to be used Confidential Information for any purpose other than that indicated in this Agreement without Abbott's prior written approval. Confidential Information shall include all Information disclosed hereunder in writing and marked "Confidential" (or, if disclosed orally, visually and/or in another form and identified at the time of initial disclosure as confidential, thereafter confirmed in a writing marked "Confidential" and provided to Salmedix within thirty (30) days of initial disclosure), as well as information materially developed as a result of such disclosure, except any portion thereof which:

   a) is known to Salmedix before disclosure thereof under this Agreement, or is independently developed by or for Salmedix, as evidenced by Salmedix' written records (except information previously disclosed to Salmedix by Abbott under a continuing obligation of confidentiality);

   b) is disclosed, without restriction, to Salmedix after full execution of this Agreement by a third party having a legal right to make such disclosure; or

   c) is or becomes part of the public domain through no breach of this Agreement by Salmedix.

4. Neither party shall disclose the existence of this Agreement or the fact that Salmedix is evaluating the Information, and neither party shall use the name of the other in any publicity or advertising without that other party's prior written approval.

5. Nothing herein shall be deemed to constitute by implication or otherwise the grant to Salmedix by Abbott of any license or other rights under any patent, patent application or other intellectual property right to or interest in the Confidential Information and any information and products materially derived or developed therefrom. Salmedix disclaims any rights and will assert no copyright, patent or other claim to the Confidential Information. Salmedix further agrees that it shall not use, develop and/or produce any of the foregoing without Abbott's prior written consent. Nothing herein shall obligate either party to enter into any other agreement and/or commercial arrangement with the other party.

6. Salmedix warrants and represents that the terms of this Agreement are not inconsistent with any other contractual and/or legal obligations it may have.

7. The period of disclosure under this Agreement shall be one (1) year from the date of full execution hereof, and may be extended by written agreement signed by the parties. Either party may terminate the period of disclosure under this Agreement without cause upon thirty (30) days' prior written notice to the other party. Termination or expiration of the period of disclosure under this Agreement shall not affect any rights or obligations which have accrued prior thereto.

8. This Agreement constitutes the entire understanding of the parties hereto with respect to the matters herein contained. This Agreement may be modified only by written agreement signed by the parties.

9. This Agreement shall be governed by and construed in accordance with the laws of the State of Illinois, excluding its conflict of laws principles.

If the foregoing terms and conditions are acceptable, as an authorized representative of Salmedix, please sign and date both originals of this Agreement and return one (1) fully-executed original to Abbott.

Very truly yours,
ABBOTT LABORATORIES

By:_____
Ake L. Johansson
Divisional Vice President
Licensing & New Business Development
Japan/PAA
Global Pharmaceutical Research & Development

Date:_____

ACCEPTED:
SALMEDIX, INC.

By:_____
Wendy Johnson
Senior Vice President
Corporate Development

Date:_____

cc: Philip Deemer, Director Corporate Licensing

CHA/JDM/Salmedix

D's Ex EG

Philip M Deemer/LAKE/CORP/ABBOTT
09/28/2001 11:48 AM

To Harriet A Mitchell/LAKE/PPRD/ABBOTT@ABBOTT
cc
bcc
Subject Update

----- Forwarded by Philip M Deemer/LAKE/CORP/ABBOTT on 09/28/01 11:49 AM -----

Philip M Deemer
09/26/01 09:29 AM

To: Ake L Johansson/LAKE/CORP/ABBOTT@ABBOTT
cc: Debra E Moore/LAKE/CORP/ABBOTT@ABBOTT
Subject: Update

Attached is my weekly update.


PMDSept24Priorities..lw

Phil Deemer *September 24, 2001*

Venture Capital Priority-1

Scope: Assess opportunity and recommend implementation plan for establishing corporate venture fund with $50 million capitalization.

Action: Benchmark with pharma and higher-tech companies. Investigate financial, organizational, and tactical aspects of potential fund.

Timeframe: Prepare presentation to management by the end of June.

Update: Presentation revised and sent to Jim Tyree on 9/20/01

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Dilaudid Oros - Priority-2

Scope: Divest Dilaudid Oros US - Retain ex-U.S. rights.

Action: Alza/J&J has stiff financial terms and co-promo and manufacturing rights making them a likely partner for divestiture. Other potential partners include Elan and Purdue Frederick. Other pain management opportunities may also be of interest to these partners including ABT963 and ABT-594. Contact Alza to discuss their existing interest (Alza made a proposal 10/00 before the FDA requested an additional trial).

Timeframe: Identify partner within 90 days (may involve package of 3 or more compounds). Complete agreement within120 days.

Update:
The New Business Development group has evaluated the financial alternatives of various senarios with Oros Dilaudid and is discussing these with senior management.

Devco Priority- 4

Scope: BTS - 74398 proposed for development by Devco with

buy-back rights or complete out-license. Final decision to be made following technical review with Devco on May 18th, 2000.

Action: Negotiate and complete agreement with Devco following decision post technical review

Timeframe: Complete agreement within 90 days after go - ahead decision.

Update: The Agreement was signed on 9/14/01

ETA's - Priority-5

Scope: Darusentan, BSF 208075, and B420627 are available for outlicense.

Action: Identify partners for Darusentan.

BSF 208075 is being discussed with Myogen (letter of intent). Proceed with Myogen to see if there is interest in a complete in-license.

Schwartz Pharma expressed possible interest in B420627. Follow-up.

Cardion and others expressed interest in ETA's. Follow-up.

Timeframe: Initiate contact with Myogen and Schwartz within 30 days and begin identifying candidates for Darusentan.

Update: Confidential and/or non-confidential information on Darusentan has been sent/discussed with Bayer, Novartis, Forest, E Merck, GlaxoSK, and AstraZeneca. Additional candidate companies have been identified and are being contacted (no response from my email to John/Bob as to not contacting these companies): Pfizer, Merck, Lilly, Centocor, Genencor, Roche, J&J, BMS, Aventis, Pharmacia. I had written Bayer off because of their situation but they responded last week and told me they were still interested and were using some outside advisors to help with the evaluation. A CDA has been negotiated with AstraZeneca but we are awaiting their signature.

The Myogen contract is nearly ready to be signed. I identified comparable deal terms and sent them to Jim Tyree asking once again for approval of the deal terms.

The Schwarz Pharma due diligence meeting took place on September 11. Schwarz remains interested in the opportunity. A draft Agreement has been prepared and sent to Schwarz on 9/24/01. We are awaiting approval of the deal terms from Jim Tyree.

Other Lower Priority Opportunities

Peg-Hirudin: Clinical studies with Peg-Hirudin are continuing in order to investigate its bleeding profile and potential use in end stage renal disease. Upon the conclusion of these studies (end of year) HPD would like the first opportunity to evaluate the fit with their renal business. The non-confidential package on Hirudin has been sent to Cardion. Cardion has responded that they are quite interested in this opportunity and they would like to know what market research data is available which I am trying to find. Also, HPD (Loreen) has asked me to meet with her regarding this opportunity on 9/4. I know she wants to reserve this opportunity for HPD but John L. wants me to proceed to identify outside interests which I am doing.

Segard: The meeting with Uli Grau went well. They are interested in licensing Segard for the US. They have asked for business terms. I told them I needed to address the business terms with our Senior management but that I would get back to him ASAP. I proposed some general deal terms to Uli Grau's company and it seems they were wanting to get the drug for practically nothing and pay practically no royalties. I am also talking with Vanguard about th is opportunity as well as NABI, Forest (not interested) and others.

Nordmark is no longer interested in this opportunity and we are closing it out now that the snakes are no longer available.

MMPI (ABT-518) A CDA has been signed with Salmedix and the conf. package sent to them.

ABT-677 CDA's have been signed with Viropharma and Arrow. A meeting with Arrow is planned for Oct. 10.

Other Knoll Pipeline Opportunities I have had inquiries from companies for two Knoll pipeline products that were in development but discontinued: BTS 67582 for diabetes (Phase II) and Amonifide for cancer (Phase II). I am having difficulty in obtaining information about these two.

D's Ex EH

Philip M
Deemer/LAKE/CORP/ABBO
TT

10/12/2001 04:08 PM

To pamela_demain@merck.com@internet
cc
bcc
Subject Licensing opportunities

Dear Pamela,

We have a number of licensing opportunities that I thought might be of interest to Merck

One of these is a phase III compound, Darusentan, from the Knoll pipeline for cardiovascular indications It is an endothelin antagonist for CHF, hypertension etc.

Another is a Phase I cancer drug that is an MMPI different from others that have been tried

A third is a late-preclinical oral anti-viral for influenza.

Another is a phase III compound for sepsis.

The last is a thrombin inhibitor (Peg-Hirudin) for dialysis patients in Phase II.

Please let me know if you are interested in receiving information about any or all of these compounds I am heading up our out-licensing initiatives with these.

Best regards,

Phil

phil.deemer@abbott.com

D's Ex EI

"Alan.Rosenthal" <ARosenthal@salmedix .com>
10/26/2001 12:57 PM

To <steve.k.davidsen@abbott.com>
cc <perry.nisen@abbott.com>
bcc
Subject ABT-518 and hematological cancer

Dear Steve:

I guess that e mail is the best way to go until we can speak later. As Perry told you, I and my company are interested initially in ABT 518 for hematological cancer although we would also explore the usual gang of suspects. I agree with you that an initial proof of principle in melanoma makes sense although we may have ways to assess myeloma as short proof of principle. I would appreciate your suggested references and your advice as appropriate. You should hear form one of my colleagues Wendy Johnson who is our business development VP. We are in contact with Phil Doemer and are anxious to explore whether our proposals are Abbott acceptable.

Regards, Alan

Alan S. Rosenthal, M.D.
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D's Ex EL

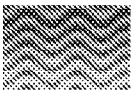
Jane A Hoff-Velk/LAKE/PPRD/ABBOTT

04/03/2002 06:29 AM

To: Azmi A Nabulsi/LAKE/PPRD/ABBOTT@ABBOTT, Daniel H Albert/LAKE/PPRD/ABBOTT@ABBOTT, Steven K Davidsen/LAKE/PPRD/ABBOTT@ABBOTT
cc: Perry D Nisen/LAKE/PPRD/ABBOTT@ABBOTT
bcc:
Subject: Salmedix

FYI

----- Forwarded by Jane A Hoff-Velk/LAKE/PPRD/ABBOTT on 04/03/2002 06:29 AM -----



Jerald J Wenker

04/02/2002 02:58 PM

To: Wjohnson@salmedix.com
cc: Jane A Hoff-Velk/LAKE/PPRD/ABBOTT@ABBOTT
Subject: Salmedix

Wendy:

Attached are answers to the questions Salmedix raised concerning ABT-518.

In addition, we would like to follow the attached agenda and we should finish in approximately two hours

- ABT-518 Overview
- Pre-Clinical Review
- Salmedix Questions
- Clinical Development
- Salmedix Questions
- Open Discussion

Jane Hoff-Velk will be coordinating the diligence efforts. I will not be able to attend.

If you have any questions please let me know. I look forward to speaking with you again soon.

Salmedix ABT518 Questions.c

JERALD J. WENKER
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ABT-518

Some Potential Questions for Abbott

Preclinical Mechanism and Biology:

1. Are there any preclinical studies specifically with ABT-518 in hematologic malignancies: myelodysplastic syndromes, lymphoma, leukemia; cell lines or animal models?

   Studies with hematologic malignancies have not been conducted. Preclinical investigations focused on solid tumor models.

Preclinical Pharmacokinetics/Pharmacodynamics:

1. What drug levels are achieved in the CNS?

   CNS levels have not been measured.

2. The pharmacokinetics suggest autoinduction via CYP3A4 pathway. How would Abbott plan to achieve chronic dosing if this pattern holds up in humans? With increasing doses given over time? Would toxicity at increasing peak plasma concentrations prove problematic?

   It is possible that dosing levels may have to be adjusted to maintain sufficient drug plasma concentrations. However, the diminished exposure to parent over time observed in preclinical pharmacokinetic studies was limited primarily to the high dose (100 mg/kg) groups, which is well above the expected efficacious dose. It is likely that the effects of autoinduction will be minimal at lower, more clinically relevant doses.

3. Given the primary metabolic pathway is CYP3A4, drug interactions will be expected, as many commonly administered drugs are eliminated via this pathway. Are there results from preclinical drug interaction studies that Abbott would be willing to share with Salmedix?

   To date no drug interaction studies have been conducted, other than those showing at least additive effects of ABT-518 when administered in combination with cytotoxic agents in tumor growth models.

4. ABT-518 is better absorbed with food (presumably an acid environment). Other MMPI competitors (past and present) have been shown to be able to be administered with or without food, but less absorbed when administered orally in patients who have taken antacids or 5HT3 antagonists. Many cancer patients are on these medications. Has Abbott conducted any antacid or 5HT3 antagonist studies in animals? If, so, could results be shared with Salmedix?

   Studies with antacids or 5HT3 antagonists have not been conducted.

Toxicology:

1. Have teratogenicity studies been conducted? If so, could results be shared with Salmedix?

   Teratogenicity studies have not been conducted.

2. What is proposed as the mechanism for the liver toxicity noted in toxicology studies?

   Increased liver weights observed in rats treated with 100 or 400 mg/kg/day were accompanied by smooth endoplasmic reticulum proliferation and are consistent with enzyme induction. This change was not evident at 10 mg/kg/day.

   Hepatic lipidosis was also observed in high-dosage animals (400 mg/kg/day) two weeks after ABT-518 was discontinued. Rats in this dosage group lost body weight during the course of drug-administration and regained weight during the recovery period. A follow-up study was conducted to better elucidate the pathogenesis of the hepatic lipidosis. In this study, particular attention was placed on mitochondrial and peroxisomal function as hepatic lipidosis may in some cases be a consequence of abnormalities in mitochondrial DNA synthesis, mitochondrial beta-oxidation pathways or fatty acid metabolism. In this follow-up study, a battery of ex vivo mitochondrial and peroxisomal assays were conducted in liver tissues of rats that had been treated with 10, 100 or 400 mg/kg/day for up to six weeks. Histologic changes similar to that noted in the previous study were again seen in 400 mg/kg/day rats (four weeks treatment, two weeks drug withdrawl period). However, there were no apparent effects on mitochondrial or peroxisomal function. In view of the lack of mitochondrial/peroxisomal changes and the fact that lipidosis was seen only during the weight gain phase after drug removal, the lipidosis is most likely a reflection of a change in nutritional state (a re-feeding effect).

3. What is proposed as the mechanism for phospholipidosis seen in multiple animal toxicology studies and what are its implications?

   Minimal to mild numbers of foamy macrophages were detected in the lungs of rats that were treated with ABT-518 in the one-month toxicity study. This change was limited to the lung and was reversible (not present at two-week recovery period). This is not an uncommon finding in the rodent and was not considered to be of toxicological significance in the studies conducted to date with this compound. No such changes were noted in the primate.

4. No toxicity was seen in the 4-week monkey study. Although this study could be repeated at higher doses, a more plausible suggestion may be to conduct a long-term (9- or 12-month) non-rodent monkey study to answer the long-term question

of whether design of a drug which presumably does not inhibit MMP1 or sheddases (TACE) eliminates the liability for joint toxicity.

For an NDA filing, the FDA now follows Japanese toxicity guidelines for chronic toxicology studies (9, instead of 12 months), but each program still needs negotiation with the agency as to which timeframe is acceptable to them.

ABT-518 does exhibit toxicity to the joints of animals in the 4-week rat study. Recent experience of Agouron/Pfizer (prinomastat), whose long-term toxicity program showed evidence of joint toxicity in 6-month rat and monkey studies, but not 4-week studies at similar doses (delayed onset), and Chiroscience's experience (BMS 275, 291) which suggests that not blocking sheddases still proved problematic for joint toxicity, longer-term toxicity studies are warranted for ABT-518 before concluding that this compound has no liability to joints, cartilage, and tendons of adults. Is Abbott willing to conduct, or cover the cost of, a 9-month monkey toxicology study with at least one dose higher than the top dose used in the 4-week monkey study?

Abbott does not believe that a 9-month study is warranted at this time. Performance of such a study will need to be evaluated following completion of the Phase I program and discussions with the FDA.

While the gelatinase selectivity of ABT-518 is greater than competitor's compounds, it is not void of MMP-1 and sheddase inhibitory activity. If inhibition of these enzymes indeed mediates joint effects, ABT-518 is likely to produce these effects in laboratory animals and in humans, *at some dose*. The key features of ABT-518 that set it apart from e.g. prinomastat are 1) its high degree of selectivity and 2) its impressive pharmacokinetic profile that avoids high peak and low trough concentrations. This is precisely the profile that is most likely to produce anticancer effects in the absence of joint toxicity.

Human Studies:

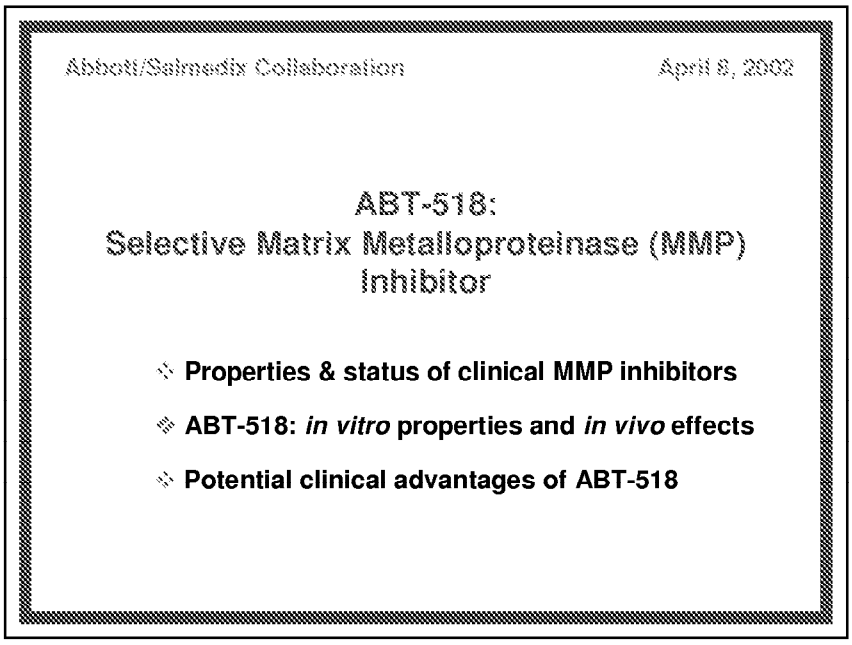
1. Given the lack of genotoxicity, and multiple interesting pharmacokinetic questions to explore, had Abbott made plans to conduct any studies with ABT-518 in normal volunteers?

   No, Abbott did not plan to perform clinical work in volunteers.

2. Other than a potential for lessened musculoskeletal toxicity in humans due to drug design, were there other advantages that Abbott saw in ABT-518 over past and current competition in the MMP field?

   Avoidance of the dose-limiting musculoskeletal toxicity exhibited by previous MMP inhibitors would provide the opportunity to achieve greater clinical efficacy.

D's Ex EM



This afternoon I'd like to speak to you about ABT-518, Abbott's gelatinase selective MMP inhibitor.

To put ABT-518 in context, I'll first cover the properties and status of other clinical MMP inhibitors.

We'll then look at ABT-518's in vitro and in vivo properties that distinguishes it from this competitors.

Finish with why we think ABT-518 may be a more appropriate tool to investigate the role of MMP inhibition in the treatment of solid tumors than previous inhibitors.

Clinical MMP Inhibitors
Selectivity versus Joint Toxicity

MMP Inhibitor Company	Development Stage; Indication	Enzyme Inhibition IC_{50} (nM) gel. A MMP-2	gel. B MMP-9	fib. col. MMP-1	TACE	Clinical Joint Toxicity
BAY 12-9566 Bayer	Phase III cancer/arthritis Discontinued	120	1,600	>30,000	>30,000	no
			highly selective			
marimastat British Biotech/ Schering-Plough	Phase III cancer Discontinued?	0.41	0.79	0.78	1.8	yes
			broad spectrum			
prinomastat Pfizer	Phase II "earlier stage" cancer	0.05	0.05	5.7	7.9	yes
			modestly selective			
BMS 275291 Bristol-Myers Squibb/ Chirosciences	Phase II/III cancer	41	25	9	"inactive"	no
			broad spectrum -- no sheddase			

As you know, enthusiasm for the MMP inhibitors field has waned recently due to the lack of efficacy of several small molecule inhibitors in Phase III studies. These compounds include BAY 12-9566, marimastat and prinomastat and, as you know, these compounds span a range of different potencies and selectivities. Bayer is highly selective, but not very potent; marimastat hits all the MMPs and TACE and prinomastat is modestly selective.

Given that Abbott's MMP inhibitor program was cultivated under Alan's auspice, I don't intend to cover the history of these compounds other than to mention two things:

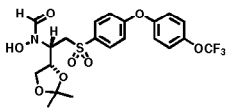
1. The lack of efficacy seen with marimastat and prinomastat we think relates to the fact that dose-limiting joint toxicity has prevented them from exploring doses that may otherwise would have been efficacious.

2. Secondly, while the lack of joint effects seen with BMS's broad spectrum/no sheddase compound suggests that it may be due to inhibition of proteinases outside of the MMP family, it is important to recognize that the cause of this joint toxicity has still not been definitively established.

Where does ABT-518 sit in this spectrum?

ABT-518 *In Vitro* Properties

Gelatinase A/B Potency & Selectivity



	Enzyme Inhibition IC_{50} (nM)						TNFα release
	gel. A MMP-2	gel. B MMP-9	fib.col. MMP-1	strom. MMP-3	matrl. MMP-7	col. 3 MMP-13	THP-1 cells IC_{50} (μM)
ABT-518	**0.78**	**0.50**	**8,900**	**12**	**11,000**	**3.3**	**> 50**
prinomastat	0.05	0.05	5.7	3.5	72	0.20	8.6
BMS 275291	41	25	9	157	23	4	> 50

- ABT-518 is more selective (gel A/B vs. fib. col./TACE) than prinomastat
- ABT-518 is more potent versus gelatinase A/B than BMS 275291

Similar to other groups, we subscribe to the idea that the gelatinases are important for tumor progression and consequently we optimized ABT-518 for gelatinase potency in lieu of activity against other MMPs and sheddases like TACE.

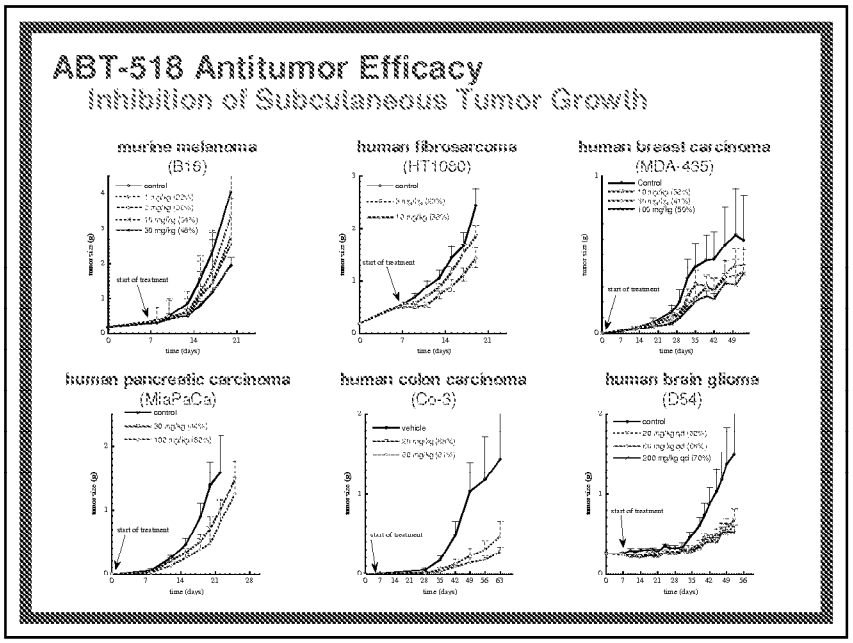
ABT-518 is a biaryl reverse hydroxamate whose structure is shown here.

As you can see from IC50 values, ABT-518 is a subnanomolar inhibitor of both gelatinases. It has some potency with respect to strom and MMP-13…. limited potency versus matrylsin and fib. coll.

It also lacks significant sheddase activity. Like the BMS compound, it has no effect on the ability of LPS to stimulate the release of TNF from THP-1 cells, which is a functional assay of TACE inhibition.

This makes ABT-518 more selective than prinomstat or marimastat and more potent versus the gelatinases than the BMS compound.

Despite this enhanced selectivity, ABT-518 produces dose-dependent suppression of tumor growth in our cancer animal models.

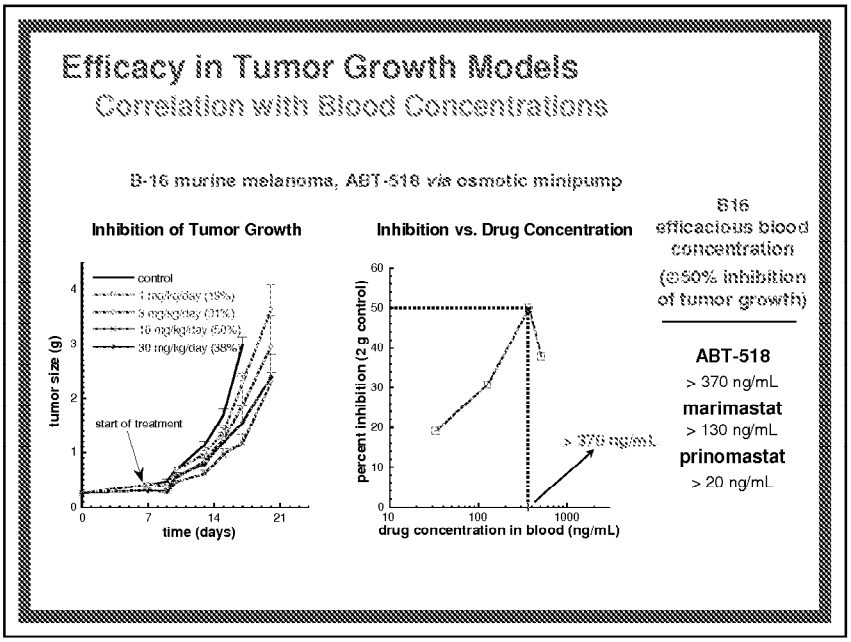


What I show here are results from six of those models - the idea is not analyze each individually, but rather to illustrate the diversity of conditions under which ABT-518 slows the growth of tumors.

These models include...

- syngeneic models, human tumor xenografts
- growth of tumor in the flank, growth of tumor at orthotopic sites
- slow growing tumors, faster growing tumors….
- dosing initiated at Day zero, dosing initiated at Day 7

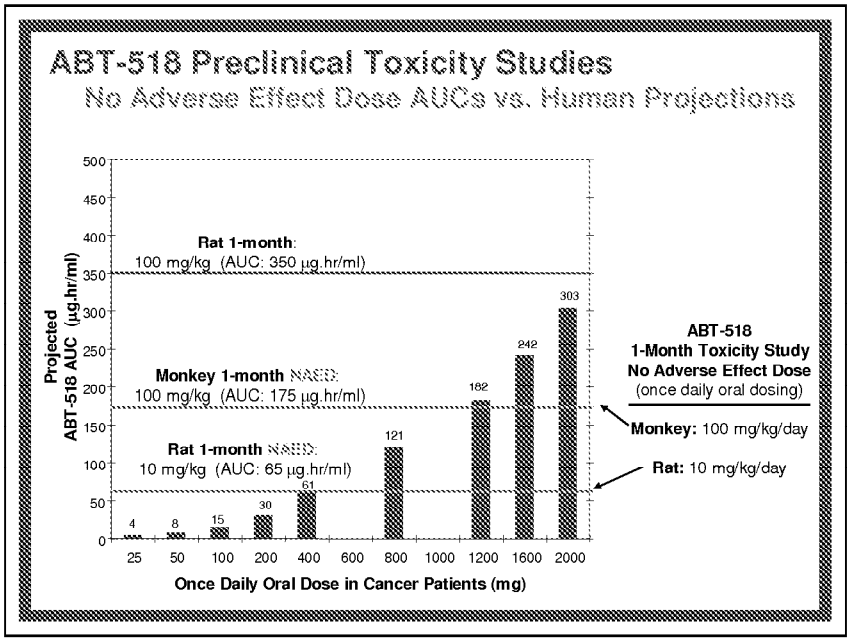
I should mentioned that in all these studies ABT-518 is given orally once or twice daily.



In an effort to establish a target concentrations of ABT-518 for clinical studies, we sought to determine the tough concentration of ABT-518 associated with efficacy in our models. You'll recall that trough MMP inhibitor concentrations are a better predictor of efficacy in cancer animal models than are, of instance, Cmax values consequently the emphasis on maintaining continous exposure in these models. We did this by carried out tumor growth studies in the B16 flank model using osmatic minipumps to achieve continuous delivery ABT-518.

Those pumps were implanted on Day 7 and produced the tumor growth curves shown here resulting in a linear relationship between efficacy and exposure up the dose that clogged the pumps. This translates into the need to maintain continuous exposure to 370 ng/mL of ABT-518 in mouse blood to produce 50% inhibition of tumor growth in this model and represents at least one measure of a target concentration for ABT-518.

Identical studies with marimastat and prinomastat have been conducted and gave efficacious concentrations of 130 ng/mL and 20 ng/mL respectively. These values will come up again when compare results from clinical trials.



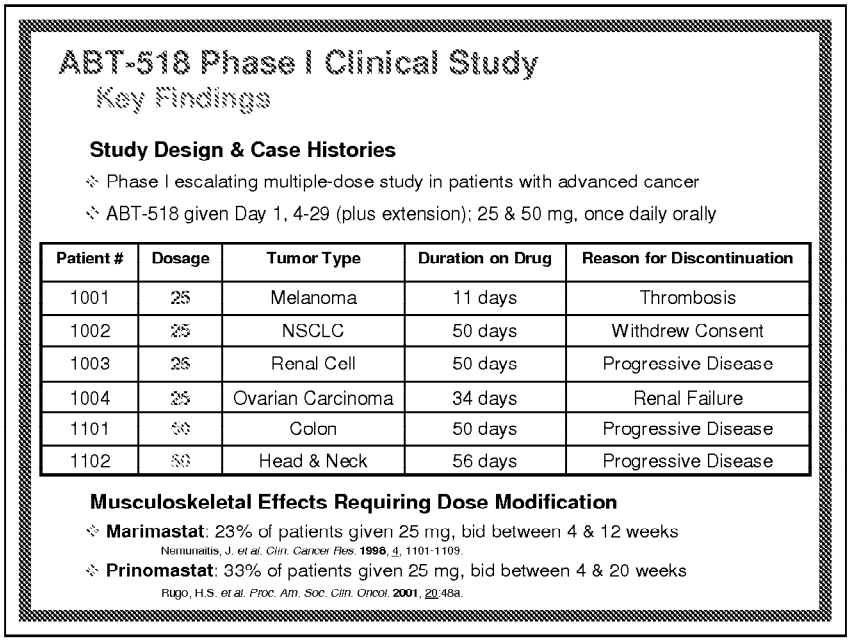
To support the clinical investigation of ABT-518 we have carried out a number of toxicity & safety studies. As you know, the compound is non-mutagenic and non-clastogenic and passed all the CV & CNS safety hurtles.

In multiple-dose toxicity studies, ABT-518 was well tolerated in monkeys given 100 mg/kg once daily for 4-weeks. In rats given 100 mg/kg over the same period we see growth plate changes and increased liver weights. Whether these constitute toxic effects is debatable, yet it is clear that we saw no observable changes in the 10 mg/kg dosing group.

What I show here are the AUCs produced by the No Toxic Effect Dose of ABT-518 in those rat and monkey studies. Those are compared to the predicted AUCs of various doses of ABT-518 in humans based on allometric scaling.

As you can see, the predicted AUCs for doses of ABT-518 up to 400 mg once daily are lower than the AUCs produced by the NTED in rat or the NTED in monkey.

That gave us the safety margin necessary to initiate a Phase I study of ABT-518 in advanced cancer patients which was commenced in March of last year, the design of which is shown here…



ABT-518 Phase I Clinical Study

Key Findings

Study Design & Case Histories

- Phase I escalating multiple-dose study in patients with advanced cancer
- ABT-518 given Day 1, 4-29 (plus extension); 25 & 50 mg, once daily orally

Patient #	Dosage	Tumor Type	Duration on Drug	Reason for Discontinuation
1001	25	Melanoma	11 days	Thrombosis
1002	25	NSCLC	50 days	Withdrew Consent
1003	25	Renal Cell	50 days	Progressive Disease
1004	25	Ovarian Carcinoma	34 days	Renal Failure
1101	50	Colon	50 days	Progressive Disease
1102	50	Head & Neck	56 days	Progressive Disease

Musculoskeletal Effects Requiring Dose Modification

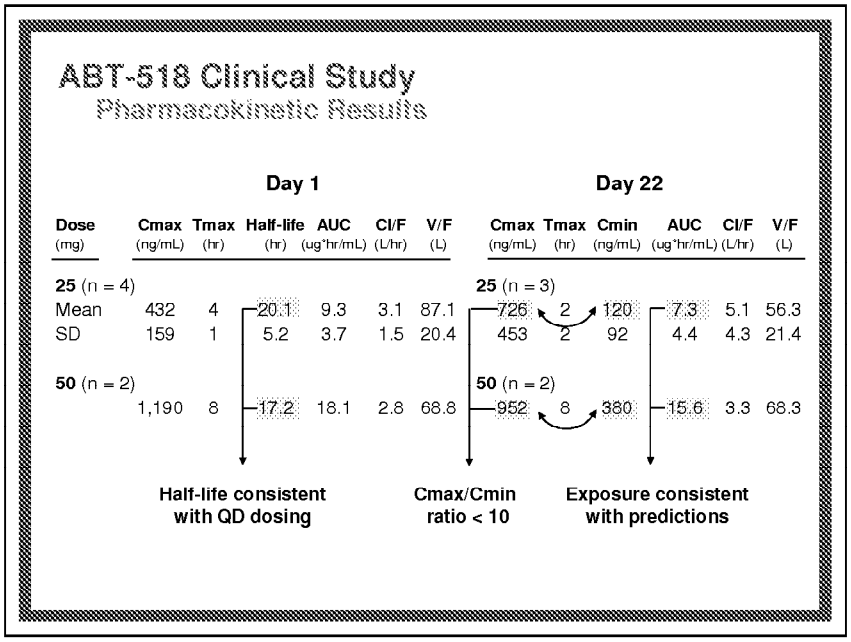
- **Marimastat**: 23% of patients given 25 mg, bid between 4 & 12 weeks
  Nemunaitis, J. *et al. Clin. Cancer Res.* **1998**, 4, 1101-1109.
- **Prinomastat**: 33% of patients given 25 mg, bid between 4 & 20 weeks
  Rugo, H.S. *et al. Proc. Am. Soc. Clin. Oncol.* **2001**, 20:48a.

This study was a multiple-dose Phase I study in patients with advanced cancer. ABT-518 was given orally once daily over one month with extension to longer periods depending on safety and disease progression.

Key Finding are shown here. We had 4 patients on the 25 mg dose for various lengths of time and two patients on the 50 mg dose for 2 months each. The compound is generally well tolerated among these patients. There was one patient with a history of thrombosis who was taken off her anti-coagulant prior to the study who suffered a thrombolytic event. This was deemed not drug related. Another 25 mg patient had undergone a nephrectomy prior to the study and suffered from elevated creatinine levels 4 weeks into the study. Whether is event was drug related has not been determined.

Significantly, what we didn't see in any of these patients is evidence of myalgia and arthralgia akin to what is seen with marimastat. One issue relates to whether we would expect to see joint effects given the number of patients and duration on drug. For comparison, the incidence of joint effects for marimastat and prinomastat are shown here. Now the incidence depends on whether you count all musculoskeletal effects or just those severe enough to cause dose modifications. If you look at just those more severe cases, for marimastat, 23% of patients require dose modifications after being given a 25 mg dose twice daily between 4 and 12 weeks. For prinomastat, 33% of patients given a 25 mg dose require holidays between 4 – 20 weeks.

So the fact that we did not see joint effects in these patients, while not definitive, is certainly encouraging. Obviously another factor that influences whether one is likely to see joint effects relates to ABT-518 exposure which is shown in the next slide.



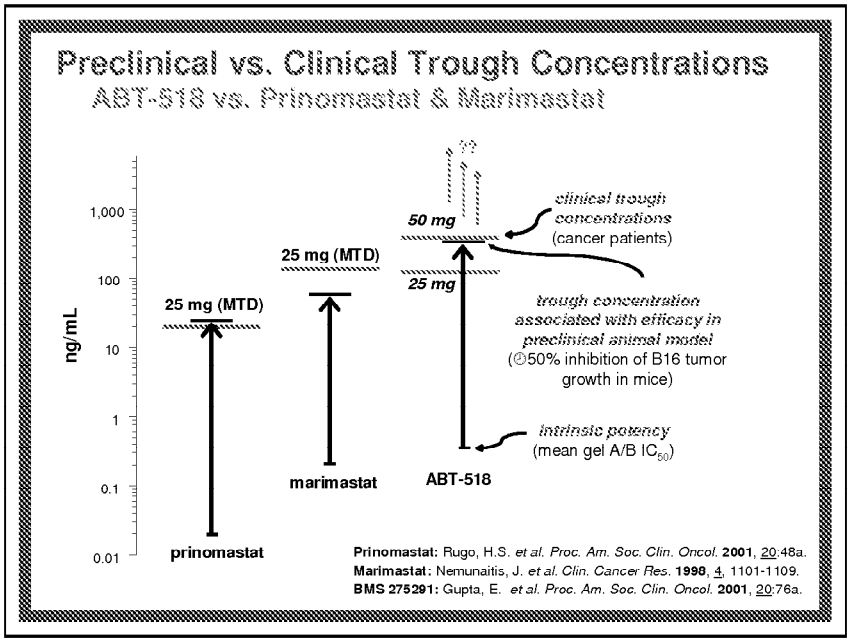
What I show here is pharmacokinetics data on the patients given 25 mg dose of ABT-518 and 50 mg dose at Day 1 and Day 22 of the study.

From both doses we see a half-life consistent with once daily oral dosing (20 & 17 hours) – this was also what was observed in dogs and non-human primates.

One of the ramifications of this extended half-life is a fairly small Cmax to Cmin ratio – here in both cases less than 10 fold. That is certainly different than prinomastat which has been shown to produce a Cmax to Cmin ratio between 30 and 50 fold in cancer patients.

If it turns out that trough concentrations correlate with MMP inhibitor efficacy and Cmax correlate with side effects like joint tox, than a diminished Cmax/Cmin ratio is precisely what one wants in an MMP inhibitor and provides ABT-518 with a clear distinguishing feature vs. the other compounds.

Finally I should point out that the mean AUCs produced by the 25 & 50 mg doses are quite close to the predicted values of 4 ughr/mL and 8 ughr/mL respectively.



Given this pharmacokinetic data and the preclinical efficacy data that I spoke about earlier, one can then being to rationalize why we think prinomastat and marimastat failed in clinical studies and why ABT-518 may not – that's shown on this slide.

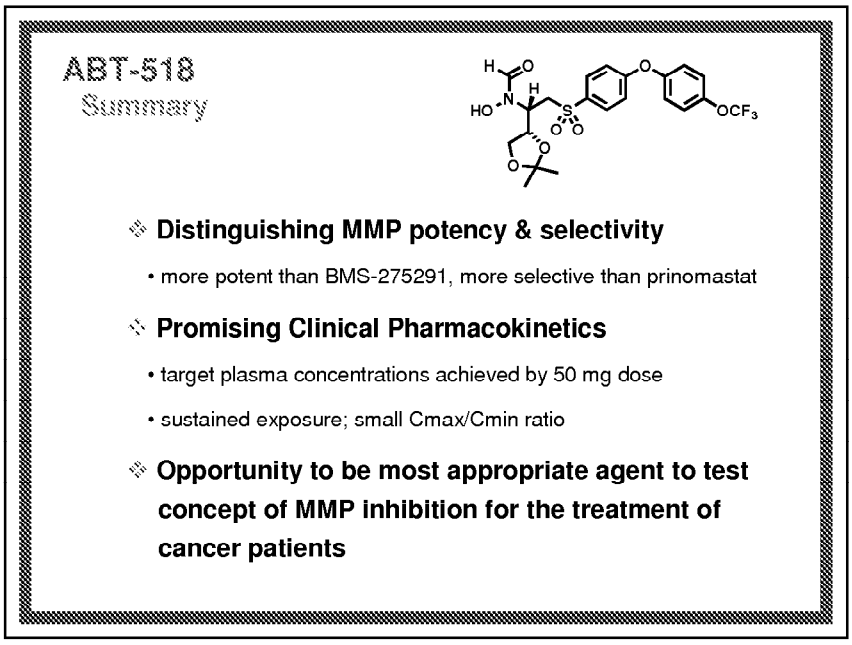
What I show here is the intrinsic potency of prinomastat versus the gelatinases relative to the blood concentration necessary to produce 50% inhibition in the B16 tumor growth model dosed as a continuous infusion… this black bar. I also show the mean trough concentration produced by a 25 mg dose of prinomastat in cancer patients… and that is shown by this red bar. The 25 mg dose of prinomastat is its MTD due to joint effects so this red bar represents a ceiling for the exposure of the drug. Clearly one would want to have the red bar be significantly higher than the black bar to have confidence of efficacy in cancer patients.

A similar shift is seen between marimastat's instrinsic potency and the conc. necessary for preclinical efficacy. The mean trough concentration produced by a 25 mg dose is shown here in red. The red bar is slightly higher than the black bar in this case, however it's important to recognize that dosing holiday's due to joint toxicity are still necessary even for patients on a 10 mg dose of marimastat.

Finally for ABT-518, we see a similar shift from intrinsic to preclinical efficacious conc. for ABT-518. The mean trough concentrations produced by the 25 and 50 mg doses of ABT-518 in cancer patients is shown by the green bars. What we're excited about is that we have achieved plasma conc. in the vicinity of those necessary for preclinical efficacy at the 50 mg dose. Again, while we haven't seen joint effects with either of these doses, the key issue here is how far up we can push this green bar with higher doses of ABT-518. If we can, I think ABT-518 is a better tool to assess the potential benefit of MMP inhibition in cancer patients than marimastat or prinomastat.

I must remind you of several caveots associated with this analysis. First our blood conc. associated with preclinical efficacy is based on a single model – one would ideally like to expand this to a number of tumor models. Second, comparing across species raises the issue of differences in protein binding and, in fact, ABT-518 is more highly protein bound in human plasma compared to mouse plasma. The extent to which this drives this black bar higher is not known. Finally, our clinical data is obviously based on a limited number of patients.

You may have notice that we haven't discussed the BMS compound in this analysis and that's because we haven't run preclinical efficacy studies with BMS 275291. Based on the lack of joint effects of the BMS compound in clinical studies, one would think that it could achieve a large separation between preclinical efficacy and mean trough concentrations. However, for those of you at the SF ASCO meeting you will have noticed that the exposure of BMS 275291 in cancer patients decreases in going from the 1,800 mg dose to the 2,400 mg dose. That was reported in this poster. Consequently, the BMS compound may have reached a ceiling of exposure, albeit for reasons different than with prinomastat and marimastat.

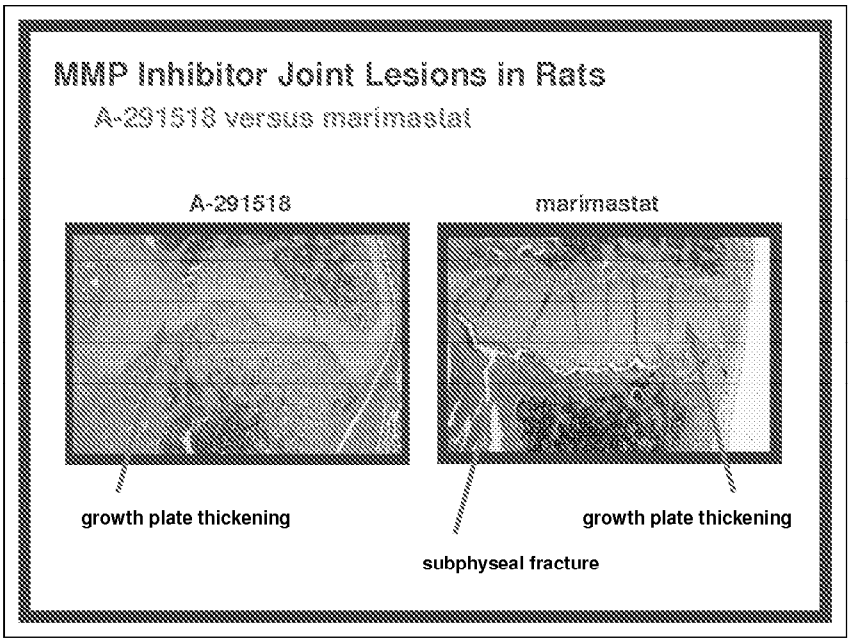


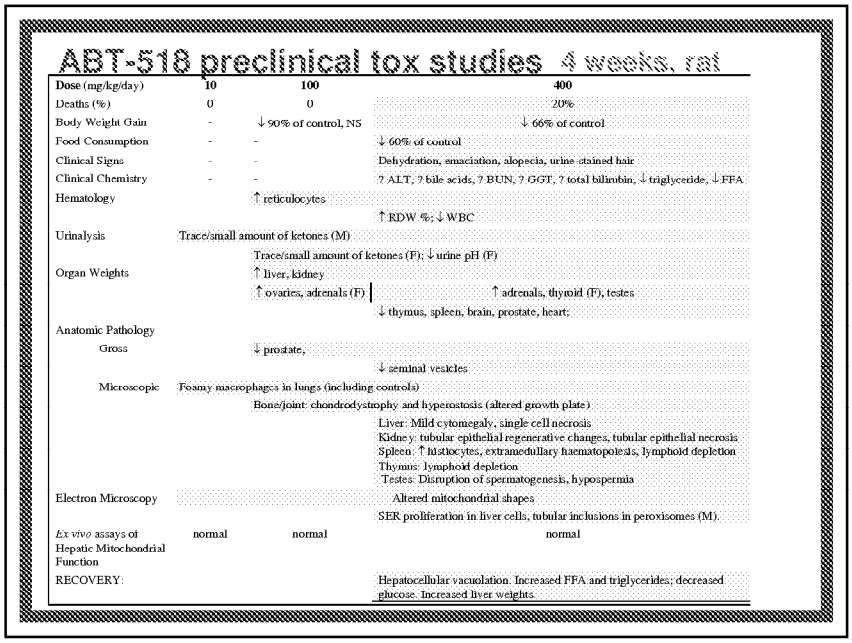
To summarize,

1. ABT-518 displays in vitro potency and selectivity that distinguishes it from other clinical MMP inhibitors.

2. It's clinical pharmacokinetics is also a distinguishing characteristic given its long half-life and small Cmax/Cmin ratio

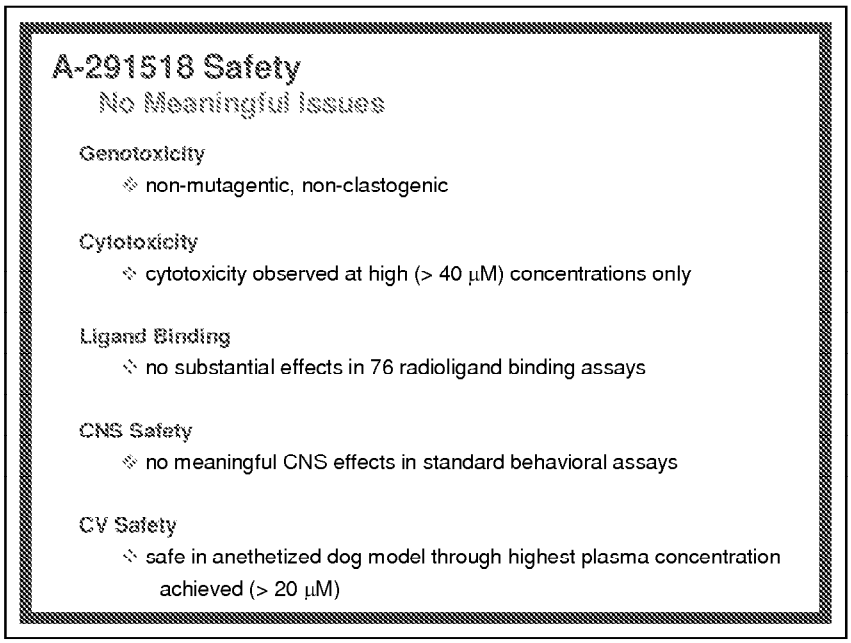
3. The lack of joint effects seen so far to suggest that we may be able to achieve sustained plasma concentrations substantially exceeding those associated with efficacy in tumor models. As a results, we feel ABT-518 has the opportunity to be the most appropriate agent to test the concept of MMP inhibition for the treatment of cancer patients.





ABT-518 preclinical tox studies 4 weeks, rat

Dose (mg/kg/day)	**10**	**100**	**400**
Deaths (%)	0	0	20%
Body Weight Gain	-	↓ 90% of control, NS	↓ 66% of control
Food Consumption	-	-	↓ 60% of control
Clinical Signs	-	-	Dehydration, emaciation, alopecia, urine-stained hair
Clinical Chemistry	-	-	? ALT, ? bile acids, ? BUN, ? GGT, ? total bilirubin, ↓ triglyceride, ↓ FFA
Hematology		↑ reticulocytes	
			↑ RDW %; ↓ WBC
Urinalysis	Trace/small amount of ketones (M)		
		Trace/small amount of ketones (F); ↓ urine pH (F)	
Organ Weights		↑ liver, kidney	
		↑ ovaries, adrenals (F)	↑ adrenals, thyroid (F), testes
			↓ thymus, spleen, brain, prostate, heart;
Anatomic Pathology			
Gross		↓ prostate,	
			↓ seminal vesicles
Microscopic	Foamy macrophages in lungs (including controls)		
		Bone/joint: chondrodystrophy and hyperostosis (altered growth plate)	
			Liver: Mild cytomegaly, single cell necrosis Kidney: tubular epithelial regenerative changes, tubular epithelial necrosis Spleen: ↑ histiocytes, extramedullary haematopoiesis, lymphoid depletion Thymus: lymphoid depletion Testes: Disruption of spermatogenesis, hypospermia
Electron Microscopy			Altered mitochondrial shapes
			SER proliferation in liver cells, tubular inclusions in peroxisomes (M).
Ex vivo assays of Hepatic Mitochondrial Function	normal	normal	normal
RECOVERY:			Hepatocellular vacuolation. Increased FFA and triglycerides; decreased glucose. Increased liver weights.



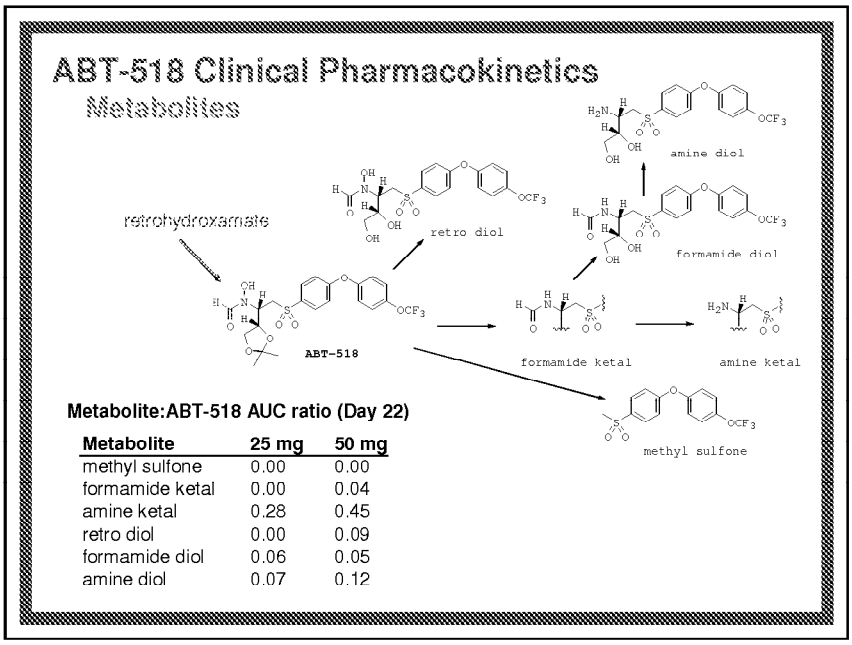
Before we go on to the toxicity studies, a couple of, fortunately brief, words about safety…..

A-291518 non-mutagenic and non-clastogenic

Cytotoxicity is observed only at high concentrations

It has no meaningful effect in a battery of 76 binding assays and no meaningful effects in standard CNS behavior assays.

And the compound is safe in an anethetized dog model of CV safety through the highest plasma concentration achieved which was in excess of 20uM.



We have studied the metabolism of ABT-770 both in vitro and using 13C-labeled material in rats and have constructed the following metabolite pathway.

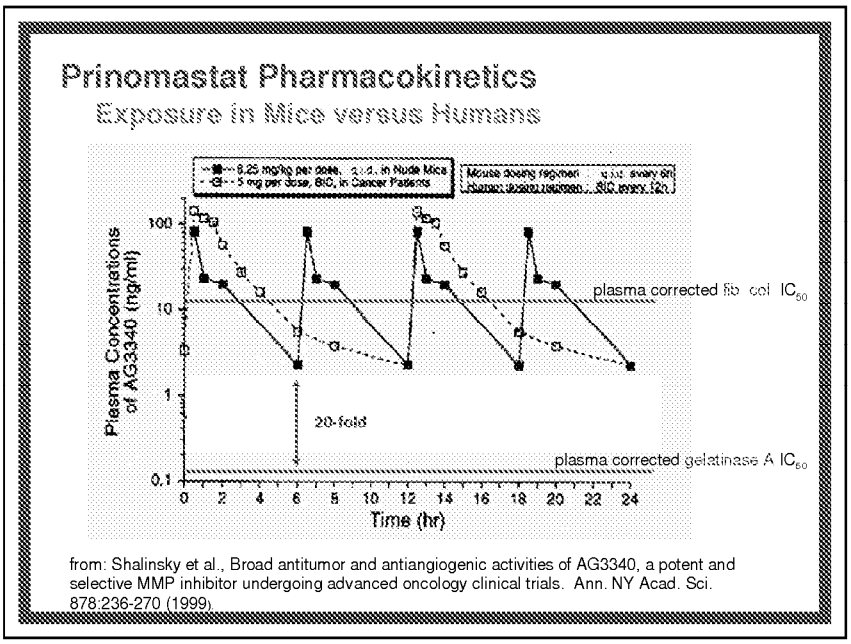
Bile duct cannulation studies suggest that the metabolitc degradation of ABT-770 is initiated by biliary elimination of its glucuronide.

Once in the gut the N-O bond of ABT-770 is reduced giving the fomramide. This is likely mediated by intestinal bacteria since incubation of ABT-770 with rat intestinal contents under anerobic conditions gives rise to the formamide. The formamide is converted to the amine by liver microsomes.

The same deformalyation initiates another pathway which ultimately produces the alcohol via the mixture of oximes shown here.

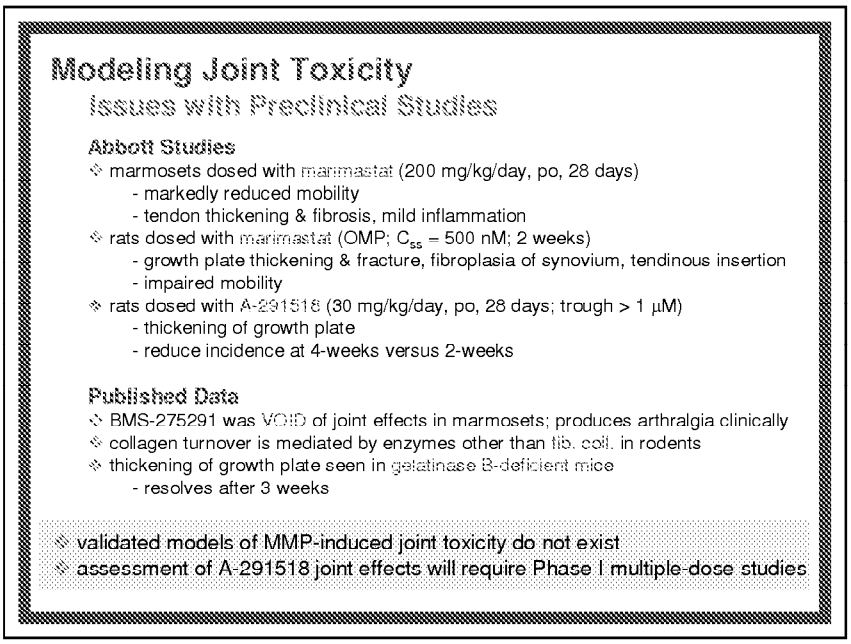
Important to recognize that all metabolites are produced by transformation of retrohydroxamate moiety which chelates zinc at active site of MMPs so none possess MMPI inhibitory activity.

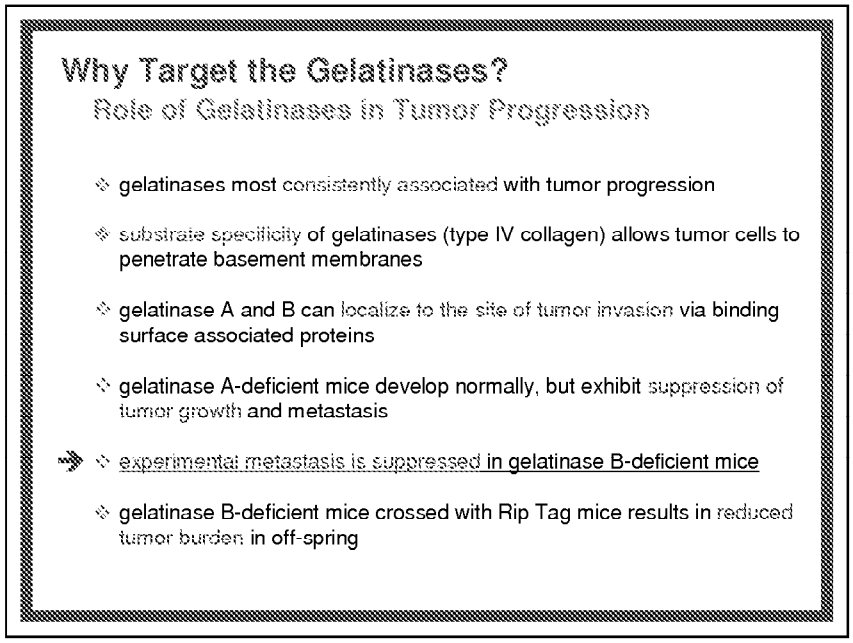
This is for ABT-770, what about the backups?



from: Shalinsky et al., Broad antitumor and antiangiogenic activities of AG3340, a potent and selective MMP inhibitor undergoing advanced oncology clinical trials. Ann. NY Acad. Sci. 878:236-270 (1999)

some MMPs more important than others…. therefore which to inhibit and which to spare?





First, relative to other MMPs, the gelatinases are most consistently associated with tumor progression based on biopsies from a # of different tumor types.

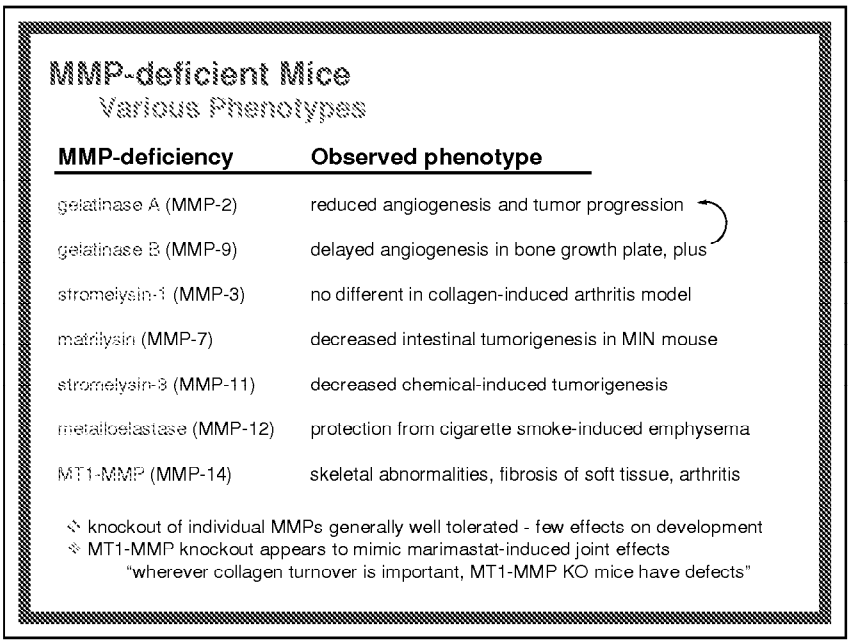
in order for tumor cells to enter vasculature, must degrade basement membranes. Type IV col. is major componenet of base. mem. and good substrate for the gels.

Gel A&B have unique ability to localize to leading egde of invading tumor cells by binding surface associated proteins….

Tumor cells implanted in gel A KO mice grow more slowly and metastasize less readily than normals….

Finally, when gel B KO mice are crossed with a stain of mice predisposed to forming pancreatic cancinomas, see a significant reduction of tumor burden in off-spring.

Based on this evidence, we'd like our compounds to inhibit the gelatinases…. BUT we'd also like to avoid broad MMP inhibition and the reason for that relates to the side effect profile of broad spectrum inhibitors currently in clincal trials...



MMP-deficient Mice

Various Phenotypes

MMP-deficiency	Observed phenotype
gelatinase A (MMP-2)	reduced angiogenesis and tumor progression
gelatinase B (MMP-9)	delayed angiogenesis in bone growth plate, plus
stromelysin-1 (MMP-3)	no different in collagen-induced arthritis model
matrilysin (MMP-7)	decreased intestinal tumorigenesis in MIN mouse
stromelysin-3 (MMP-11)	decreased chemical-induced tumorigenesis
metalloelastase (MMP-12)	protection from cigarette smoke-induced emphysema
MT1-MMP (MMP-14)	skeletal abnormalities, fibrosis of soft tissue, arthritis

- knockout of individual MMPs generally well tolerated - few effects on development
- MT1-MMP knockout appears to mimic marimastat-induced joint effects
  "wherever collagen turnover is important, MT1-MMP KO mice have defects"

some MMPs more important than others…. therefore which to inhibit and which to spare?

D's Ex EN

Jane A Hoff-Velk/LAKE/PPRD/ABBOTT

04/16/2002 06:41 AM

To: Azmi A Nabulsi/LAKE/PPRD/ABBOTT@ABBOTT, Steven K Davidsen/LAKE/PPRD/ABBOTT@ABBOTT, Sherry J Morgan/LAKE/PPRD/ABBOTT@ABBOTT, Daniel H Albert/LAKE/PPRD/ABBOTT@ABBOTT, Raymond A Knight/LAKE/PPRD/ABBOTT@ABBOTT, Perry D Nisen/LAKE/PPRD/ABBOTT@ABBOTT, Gayle A Kirkpatrick/LAKE/GPRD/ABBOTT@ABBOTT, Kurt Wehrle/LAKE/GPRD/ABBOTT@ABBOTT

cc:

bcc:

Subject: Salmedix

Please see Jerry's note below. In addition, I would like to thank each of you for working so diligently to clearly present this opportunity to Salmedix. I greatly appreciate everyone's efforts!!
Jane

----- Forwarded by Jane A Hoff-Velk/LAKE/PPRD/ABBOTT on 04/16/2002 06:39 AM -----

Jerald J Wenker

04/15/2002 04:46 PM

To: Jane A Hoff-Velk/LAKE/PPRD/ABBOTT@ABBOTT
cc: Suzanne Lebold/LAKE/PPRD/ABBOTT@ABBOTT
Subject: Salmedix

Jane:

I wanted tolet you know that I spoke with Wendy Johnson at Salmedix today. After their review, Salmedix has decided they do not have interest in ABT-518. The risk of development, side effect profile, and lack of dollars at Salmedix were primary reasons.

If you have any questions, please let me know. Please thank the team that worked on the project We will continue to pursue with other interested parties.

JERALD J. WENKER
Divisional Vice President
Abbott Laboratories
Global Licensing and New Business Development -- Americas
200 Abbott Park Road: AP34; D: R50C
Abbott Park, IL 60064-6189
847 938-2962

D's Ex EO

John G Poulos/LAKE/GPRD/ABBOTT
05/03/2002 08:55 AM

To Noula A Ducato/LAKE/PPRD/ABBOTT@ABBOTT
cc
bcc
Subject April highlights

Noula,

Please Print.

John Poulos
Divisional Vice President
Global Licensing and New Business Development
Abbbott Laboratories
Phone: 847-938-7598
Fax: 847-938-6807
----- Forwarded by John G Poulos/LAKE/GPRD/ABBOTT on 05/03/2002 08:57 AM -----

Natalie Szczerbak
05/02/2002 04:00 PM

To: Jerald J Wenker/LAKE/GPRD/ABBOTT@ABBOTT, Ake L Johansson/LAKE/GPRD/ABBOTT@ABBOTT, John G Poulos/LAKE/GPRD/ABBOTT@ABBOTT
cc:
Subject: April highlights

Please review and edit the April highlights. Since the highlights been updated, please focus on the red and blue text which reflect questions on the specific information. Highlights are due to Jim on Monday. Please send me your edits on Fri. Thanks.


April draft.doc

BLUE – old news to be updated
RED – questions to be answered

RE: April 2002 Highlights

I. CONCLUDED BUSINESS

Project Acorn (Co-promo): A co-promotion of Amevive within Latin America declined by Biogen due to concerns regarding competition from D2E7 in psoriasis and rheumatoid arthritis.

II. PENDING FINAL RESOLUTION

Project Dakota (Partnering): Discussions for a potential deal structure with Novartis continues. A review meeting with senior management is scheduled for the week of May 6th for a go-no/go decision.

Project Galleon (Co-promo/mkt): The negotiations with Grunenthal on a co-promotion/marketing arrangement in Europe for Gatifloxacin (a quinolone) are on hold. The European regulatory authority has limited indications and contraindicated gati for diabetics. Several important countries have elected not to approve. We have requested more information on the details of the objections and decision.

Project Gladiator - (Acquisition): An updated analysis for the acquisition of the GSK Anesthesia business in Europe was prepared and issued to Al management. A review meeting is scheduled in JUNE? to discuss this opportunity.

Project Belt (Co-promo/mkt): Negotiations are ongoing for a co-promotion / co-marketing agreement for oral levosimendan. Abbott has proposed a term sheet and is waiting for a response from Orion.

Project Geometry (Co-develop/promo): A worldwide co-promotion of a combination of Tenofovir (approved drug) and Coviracil (FTC) for HIV (not yet approved) is financially modeled based upon preliminary deal terms provided by Gilead accounting for the preexisting Abbott / Triangle legal agreements. Discussions between Gilead, Triangle, and Abbott are scheduled for MAY?

Project Garden (Gengraf Divestiture): Second offer by Sangstat determined to be non-viable due to significant difference in valuations between parties on Gengraf. Of the ten companies contacted for divestiture of Gengraf on a worldwide basis with Abbott retaining manufacturing rights, AMSA Pharmaceuticals and Quintiles are evaluating the opportunity.

Project Viper (Divestiture): Preliminary non-binding deal terms have been received from multiple parties for the divestiture if Vicoprofen. The current financial terms may result in favorability vs Plan for Abbott. Next steps include???

Project Elbow (Co-promo / Co-Market): A co-promotion / co-market agreement of Escitalopram for depression within Latin America is being negotiated. Both partied have proposed counter offers and an agreement in concept has been reached. The current financially modeled terms reflects an approximate 40% split to Abbott, 60% split to Lundbeck. Due diligence is being scheduled for May.

Project Zeus: Currently being negotiated with execution targeted for June.

Project Gyro (Co-promo/Acquisition): Acquisition and co-promotion models have been constructed for Advicor (combination product consisting of lovastatin and Niaspan) and Niaspan (an extended release niacin), approved drugs for CV lipid lowering in the US. KOS announced (1/02) a strategic commercialization agreement with Quintiles which provided an additional sales force of 150 (beyond base 300) cardiovascular-trained representatives for two years. A go no-go decision is scheduled for April.

Omnicef(Contract Renegotiation): Discussions have been initiated with Fujisawa regarding the bulk price and royalty rate for Omnicef in the US. The objective is to reach an agreement no later than the end of Q2/02.

Angiogen – Novel Use for r-UK (License): PEMC approved the licensing of the exclusive rights to Angiogen's intellectual property using recombinant urokinase (ABT-120) to generate angiostatin for use in oncology. Abbott will initiate an open-label, randomized, dose-escalating safety and tolerability Phase I study of ABT-120 (r-UK) in subjects with solid tumors.

Banyu - J 107088 (Option/License): PEMC approved the option agreement for the Phase I DNA topoisomerase inhibitor I. The execution of the option agreement is pending.

Cyclacel - Novel Anti-mitotic Compounds (Oncology Collaboration/License): Cyclacel proposed a term sheet for the collaboration. Pending the IP diligence, theis opportunity will be reviewed by Discovery by the end of 2Q02.

Esperion ETC588 & ETC642 (License): Due to toxicology and safety concerns this opportunity has been declined.

Amylin AC-2993 (License): This Phase III compound is an agonist of GLP-1 that exhibits glucose lowering effects in vivo. Data currently being reviewed by Millennium. Next steps ....?

Idun (Acquisition): A preliminary acquisition analysis is ongoing. The data package will be reviewed with senior management XX?

Trigen - TRI50b (License): Information requested by Abbott was received from Trigen. Material is being held until direction regarding Abbott's strategic interests in clinical stage cardiovascular opportunities is received.

Biostratum – Pyridorin (License): This compound is in Ph II clinical trials for diabetic neuropathy. Abbott has made company contact and is pursuing additional information for review.

Fournier - LF 200688 & LF200337 (License): Pre-clinical for the treatment of type 2 diabetes. Per discussions with the company in February, updated information regarding PPAR alpha activation will not be available until April 2002. Further activity by SA on hold, pending the availability of additional data.

Regeneron – Axokine (License): This product is in Phase III clinical trials for the treatment of obesity. Further action by SA on hold pending BD review/commercial assessment.

Merck Lipha (CRE-16336): CRE-16336 is an insulin sensitizer which is in phase II clinical development for the treatment of type 2 diabetes and insulin resistance. A meeting will be scheduled during 3Q02.

Probiodrug (P32/98 + backups): A meeting was held on March 15, 2002 to discuss licensing opportunities for DPP-IV inhibitors for type 2 diabetes. Scientific technical assessment pending. eived package of information on April 24, 2002; distributed to Abbott group to review.

PPD Discovery – Cancer Markers (Collaboration/License): The decision from the Cancer Discovery group was not to proceed forward. This was communicated to the company.

Protein Design Laboratories – Zamyl & Remitogen (License): Zamyl, a Phase III antibody, was declined due to concerns about safety and efficacy.

Salmedix (Outlicense): Meeting held in San Francisco to review data with Salmedix. They have declined the opportunity to license ABT-518.

ABT-598 (Outlicense): Following the review of non-confidential information Pfizer declined to pursue further discussions due to concerns over the potential narrow therapeutic window. FIVE?? other companies will be contacted by 3Q02 to out-license ABT-598.

Biosynexus - BSYX-A110 (License): This opportunity will be reviewed at the May 8th PEC meeting and will include a technical diligence report for this chimeric antibody for the prevention of sepsis in low birth weight neonates.

BMS- LEA29Y (License/Co-promo): Confidential information for BMS-LEA29Y, a Phase II fusion protein for organ transplant and RA has been received. A list of technical questions was sent to BMS and a follow-up meeting will be scheduled for the week of MAY X??.

ICOS - IC485 (License/Co Mkt/Co Develop): Confidential scientific and clinical information under review documents forr the Phase I, PDE4 inhibitor prior to a follow-up meeting on May 14th.

Immune Response (Remune therapeutic vaccine for HIV) – Based on the scientific, regulatory and manufacturing review, this opportunity will be declined. Significant hurdles exist in all areas.

Ranbaxy Clarithromycin Formulation: Scale up study to be performed by Ranbaxy by WHEN. Next steps include demonstration of bio-equivalence with and with/out food for Ranbaxy's clari formulation.

Hydra (Equity and Research Collab): The elastin oligopeptide-coated stent research collaboration agreement is completed. The CatSper ion channel research agreement will be executed MAY X. Both research agreements include option rights to products. Hydra's Series A was closed 4/3/02. Abbott will participate in the Series A as an additional investors ($1.3mm) at the execution of both research agreements.

Abgenix (Transgenic mouse technology and mAb Targets) Proposal to license Abgenix's Xenomax transgenic mouse technology. Abgenix has confirmed the availability of IL-12 as a target, finalizing key terms. Discussions on targets in oncology and inflammation are on-going.

Medarex (Transgenic mouse): Proposal to license Medarex's KM mouse technology for an unlimited number of targets. A draft agreement is currently under review.

Diversys (Antibody Platform Technology): ABC and Diversys are negotiating key terms for an option to the Diversys technology to follow a proof of concept experiment for their dual specific antibody technology. A meeting is scheduled for April 5 to review outstanding terms prior to recommending to move forward.

Cambridge Antibody Technology (Phage Display): CAT visited ABC in March and delivered a draft of the library license. ABC proposed a technology swap in which CAT could obtain access to Abbott's yeast display IP, in exchange for access to all of the CAT MRC IP. Meeting to discuss proposal planned at CAT in May.

I. NEW INITIATIVES

Novo Nordisk: A comprehensive product and R&D pipeline analysis was conducted in preparation for a May 7th meeting with Novo Nordisk.

Asahi Kasei – ART-123: Confidential information for the Phase II thrombomodulin inhibitor, ART-123, is being reviewed. Asahi is seeking a partner for development and marketing for territories outside Japan.

Fujisawa – Omnicef: Discussions were initiated with Fujisawa regarding the bulk price and royalty rate for Omnicef in the US. The objective is to reach an agreement no later than the end of Q2/02.

Hypnion (Discovery collaboration): A follow up meeting planned for June to determine interest in CNS genomics company.

Biovail (In-license): A meeting planned for May 16 to discuss CR Tramadol opportunity in moderate pain.

Durect (In-license): A meeting planned for May 21 to discuss depot and pump delivery technologies for pain.

Acadia (In-license): Internal testing of Acadia's preclinical 5HT2 inverse agonist, ACP-103 for schizophrenia will be completed in May and a follow up meeting to discuss results is scheduled for June.

Baylor Medical School/Clayton Foundation: Research collaboration with Dr. Wakil regarding ACC-2 (DESCRIBE) and FASN under negotiation.

Biovitrum: The Company has been approached regarding Abbott's interest in their 11- HSD program which includes BVT-3498.

University of Edinburgh: The university technology transfer office has been contacted regarding their licensing strategy (non-exclusive, discovery) for their 11-HSD patent estate.

ZymoGenetics: The company has been contacted several times over the last 6 months, regarding their licensing strategy (non-exclusive, discovery) for their glucagon receptor patent estate.

Henneman Patents: Brahms AG holds the Henneman patents for combinations of T3/T4 where T3 is released in a controlled formulation.

Mutual Pharmaceuticals: This unique technology could potentially allow for an alternate in Synthroid lifecycle management. Next steps include a comprehensive evaluation of all Synthroid life-cycle management formulation companies.

Therics: A meeting was held on April 25 to evaluate Therics's technology and pharmaceutical formulations capabilities which could potentially be applied to Synthroid. The next steps include an evaluation of all Synthroid life-cycle management formulation companies.

Delsys/Elan: Thyroid lifecycle management: CDA completed and confidential information received and distributed to internal team. Delsys visited Abbott on April 9, 2002. Next steps: caucus with Abbott team to evaluate all the Synthroid life-cycle management formulation companies.

ABT-318 (Outlicense): Two, potentially three, companies have expressed an interest in licensing the anti-mitotic ABT-318, a back up to ABT-751. A confidential package is being developed to provide information to interested parties.

AnorMed – AMD0473 (License): Non-confidential information was received on this platinum compound for a CDA will be executed to obtain confidential information.

Eos – Antibody targets (Collaboration/License): Interest expressed by Oncology Discovery to review the portfolio of Eos since they just recently lost their partner, Pharmacopoiea. Contact was made and we are scheduled to have a videoconference with them under a CDA in early May.

Genzyme Molecular Oncology (GMO) – Anti-Angiogenic Targets (Collaboration/License): Contact to be made in May. Determined CDA was not sufficient in covering Abbott Park discussions.

Kosan – Epothilone D (License): Information on Kosan was given to Jerry Wenker, so he could make initial contact. Epo D is in Phase I and was highlighted in LSP. In addition, Saul Rosenberg expressed additional interest after reviewing data at AACR.

Neotherapeutics - Satraplatin (License): Confidential information under review for this oral platinum compound. Neotherapuetics is interested in ABT-518.

Tularik Pharmaceuticals – Cancer Markers (Collaboration/License): Interest was expressed by the Cancer Discovery group. After a discussion between Steve Fesik and Terry Rosen (Tularik), a similar collaborative deal alignment was determined. Information was sent by Tularik concerning resources/headcount they would be willing to provide. The next step is for us to determine what they want from a business prospective. This will be determined in May.

GenMab - Humax-CD4 (Co develop/Co mkt): A non-confidential brochure for this anti-CD4 huMAb in Phase III for anti-TNF refractory RA is undergoing pre-clinical and clinical review. Additional discussions may take place with GenMAb in June/July when their current large Phase II study is completed.

Scios - SCIO-469 and Boehringer-Ingelheim - BIRB 796 – Both companies have Phase II p38 kinase inhibitors for RA.

Serono - Rebif (beta-interferon): A letter has been sent to Serono to determine their interest in partnering Rebif, which was recently approved for MS in the U.S.

Coley: Confidential information on use of CpG oligonucleotides as immune stimulants for treatment of HCV and HIV is under evaluation. Coley has requested a strategy review presentation from Abbott followed by a proposal by end of May. Assessment team selected and initial review of commercial, regulatory manufacturing and scientific areas underway.

Vertex: Non-confidential information received on Gyrase B inhibitors (potential broad spectrum anti-infectives). Initial evaluation was favorable and visit to review confidential packet has been scheduled.

Solubest: Very preliminary confidential data received on an alternative formulation of Clari reviewed by scientific team. Will need to see animal data in order to make further evaluation.

D's Ex EP

John P FitzGerald /LAKE/PPRD/ABBOTT
Sent by: John P FitzGerald

08/02/2002 09:20 AM

To: Steven K Davidsen/LAKE/PPRD/ABBOTT@ABBOTT, Matthew J Rieser/LAKE/PPRD/ABBOTT@ABBOTT
cc: Jerald J Wenker/LAKE/GPRD/ABBOTT@ABBOTT, Perry D Nisen/LAKE/PPRD/ABBOTT@ABBOTT, Steve Fesik/LAKE/PPRD/ABBOTT@ABBOTT, Saul H Rosenberg/LAKE/PPRD/ABBOTT@ABBOTT, Jane A Hoff-Velk/LAKE/PPRD/ABBOTT@ABBOTT
bcc:
Subject: ABT 518 Outlicense Status

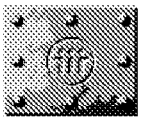
Steve / Matt,

Due to the lack of interest in ABT 518 we currently will not be moving forward with out-licensing initiatives. After canvassing a larger group, we heard back from5-6 parties who had no interest in the compound.

Best regards,

John

D's Ex EQ



Azmi A Nabulsi /LAKE/PPRD/ABBOTT
Sent by: Diane L McDermott

08/13/2002 04:48 PM

To: Anne E Hagey/LAKE/PPRD/ABBOTT@ABBOTT, Atulkumar P Ramaiya/LAKE/PPRD/ABBOTT@ABBOTT, Ingrid B Joseph/LAKE/PPRD/ABBOTT@ABBOTT, Lori V Rountree/LAKE/PPRD/ABBOTT@ABBOTT, Renee Greco/LAKE/PPRD/ABBOTT@ABBOTT, Rod A Humerickhouse/LAKE/PPRD/ABBOTT@ABBOTT, Saul H Rosenberg/LAKE/PPRD/ABBOTT@ABBOTT, Susan M Glad/LAKE/PPRD/ABBOTT@ABBOTT, Rick Lesniewski/LAKE/PPRD/ABBOTT@ABBOTT, Steven K Davidsen/LAKE/PPRD/ABBOTT@ABBOTT

cc:

bcc:

Subject: John Hopkins Cancer Center and Abbott Oncology Collaboration Meeting

John Hopkins Cancer Center and Abbott Oncology Collaboration Meeting
Date: August 14, 2002
Time: 1:30-5:30
Location: AP30-3 SE Oncology Group Conference Room

Johns Hopkins-Attendees:

Michael Carducci M.D.- Associate Professor of Oncology and Urology; Co-Director, Drug Development Program

W. Thomas Purcell, M.D.- Instructor in Oncology

Michelle Rudek PharmD, Ph.D.- Research Associate; Associate Director of Analytical Pharmacology Core Lab

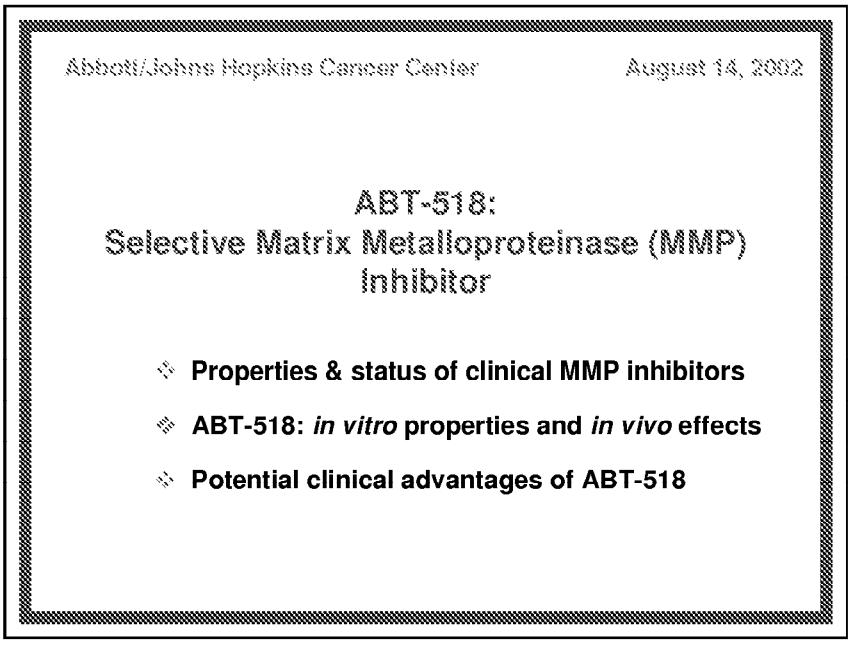
Discussion of proposed collaboration studies

- atrasentan studies
  - atrasentan & Zometa in renal cell or breast patients with bone mets/ Roberto Pili
  - Kinetics study/ Michelle Rudek
- ABT-510 studies
  - 1st line Colon cancer/ Tom Purcell
  - ECOG interact / Michael Carducci
- ABT-751
  - Taxane resistant PCa / Michael Carducci
- Compounds in early development
  - ABT-518 MMPI 10 min.

- FTI 10 min.
- Other compounds in pipeline/ Perry

- Non Clinical Collaborations discussio

D's Ex ER



This afternoon I'd like to speak to you about ABT-518, Abbott's gelatinase selective MMP inhibitor.

To put ABT-518 in context, I'll first cover the properties and status of other clinical MMP inhibitors.

We'll then look at ABT-518's in vitro and in vivo properties that distinguishes it from this competitors.

Finish with why we think ABT-518 may be a more appropriate tool to investigate the role of MMP inhibition in the treatment of solid tumors than previous inhibitors.

Clinical MMP Inhibitors

Selectivity versus Joint Toxicity

MMP Inhibitor Company	Development Stage; Indication	Enzyme Inhibition IC_{50} (nM) gel. A MMP-2	gel. B MMP-9	fib. col. MMP-1	TACE	Clinical Joint Toxicity
BAY 12-9566 Bayer	Phase III cancer/arthritis Discontinued	120	1,600	>30,000	>30,000	no
			highly selective			
marimastat British Biotech/ Schering-Plough	Phase III cancer Discontinued?	0.41	0.79	0.78	1.8	yes
			broad spectrum			
prinomastat Pfizer	Phase II "earlier stage" cancer	0.05	0.05	5.7	7.9	yes
			modestly selective			
BMS 275291 Bristol-Myers Squibb/ Chirosciences	Phase II/III cancer	41	25	9	"inactive"	no
			broad spectrum -- no sheddase			

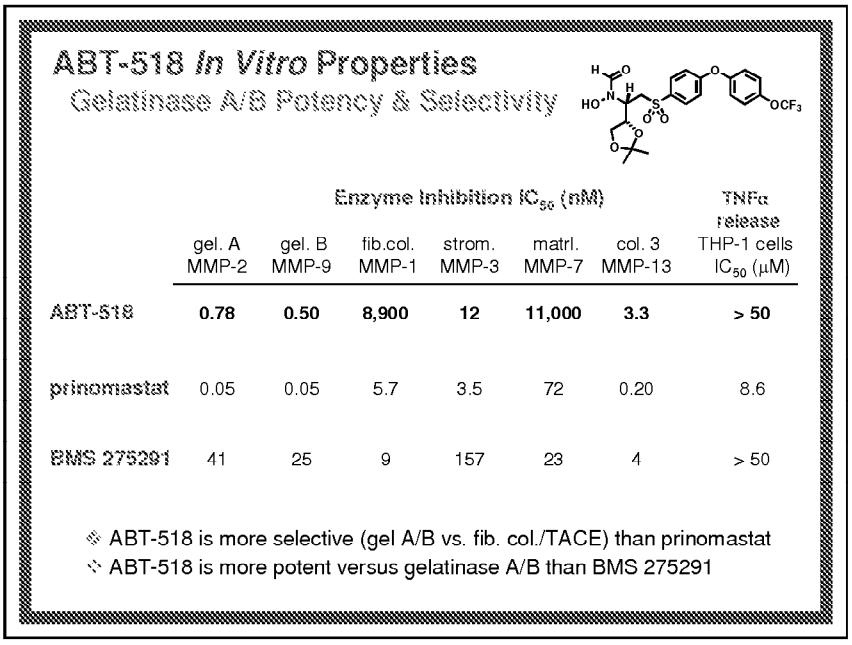
As you know, enthusiasm for the MMP inhibitors field has waned recently due to the lack of efficacy of several small molecule inhibitors in Phase III studies. These compounds include BAY 12-9566, marimastat and prinomastat and, as you know, these compounds span a range of different potencies and selectivities. Bayer is highly selective, but not very potent; marimastat hits all the MMPs and TACE and prinomastat is modestly selective.

Given that Abbott's MMP inhibitor program was cultivated under Alan's auspice, I don't intend to cover the history of these compounds other than to mention two things:

1. The lack of efficacy seen with marimastat and prinomastat we think relates to the fact that dose-limiting joint toxicity has prevented them from exploring doses that may otherwise would have been efficacious.

2. Secondly, while the lack of joint effects seen with BMS's broad spectrum/no sheddase compound suggests that it may be due to inhibition of proteinases outside of the MMP family, it is important to recognize that the cause of this joint toxicity has still not been definitively established.

Where does ABT-518 sit in this spectrum?



Similar to other groups, we subscribe to the idea that the gelatinases are important for tumor progression and consequently we optimized ABT-518 for gelatinase potency in lieu of activity against other MMPs and sheddases like TACE.

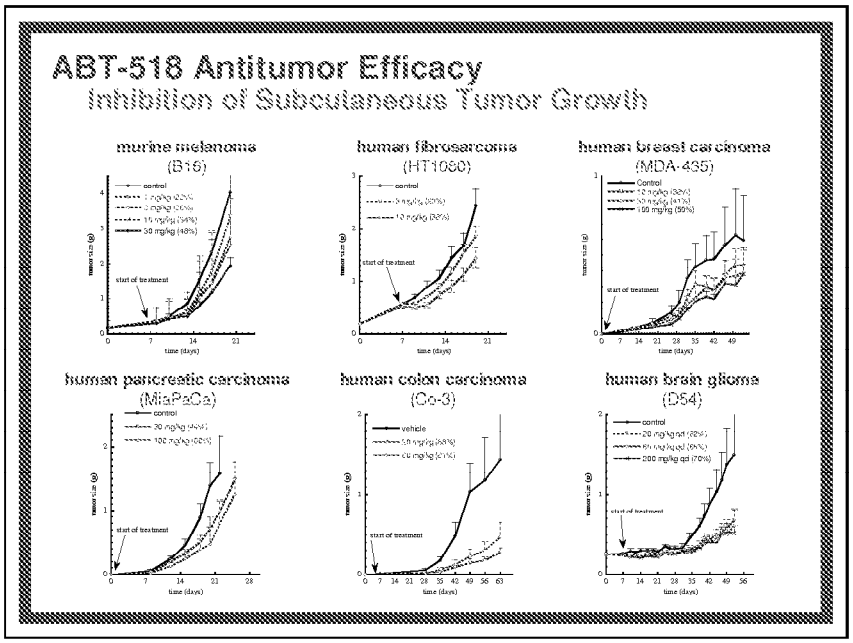
ABT-518 is a biaryl reverse hydroxamate whose structure is shown here.

As you can see from IC50 values, ABT-518 is a subnanomolar inhibitor of both gelatinases. It has some potency with respect to strom and MMP-13…. limited potency versus matrylsin and fib. coll.

It also lacks significant sheddase activity. Like the BMS compound, it has no effect on the ability of LPS to stimulate the release of TNF from THP-1 cells, which is a functional assay of TACE inhibition.

This makes ABT-518 more selective than prinomstat or marimastat and more potent versus the gelatinases than the BMS compound.

Despite this enhanced selectivity, ABT-518 produces dose-dependent suppression of tumor growth in our cancer animal models.

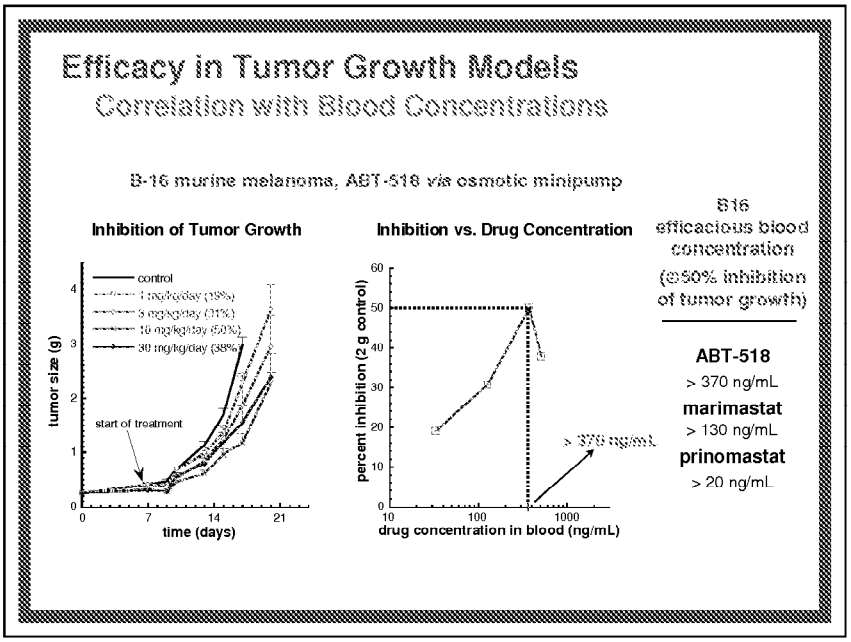


What I show here are results from six of those models - the idea is not analyze each individually, but rather to illustrate the diversity of conditions under which ABT-518 slows the growth of tumors.

These models include...

- syngeneic models, human tumor xenografts
- growth of tumor in the flank, growth of tumor at orthotopic sites
- slow growing tumors, faster growing tumors….
- dosing initiated at Day zero, dosing initiated at Day 7

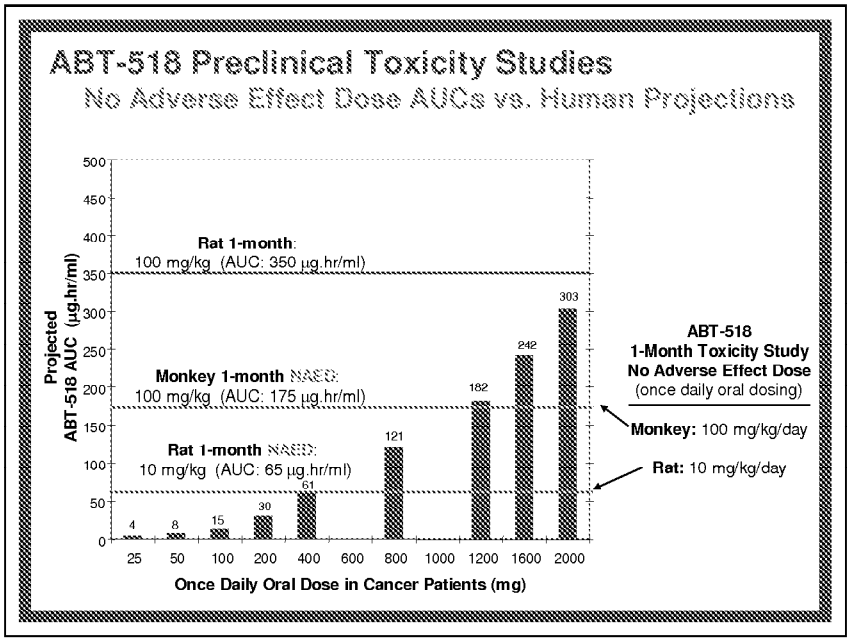
I should mentioned that in all these studies ABT-518 is given orally once or twice daily.



In an effort to establish a target concentrations of ABT-518 for clinical studies, we sought to determine the tough concentration of ABT-518 associated with efficacy in our models. You'll recall that trough MMP inhibitor concentrations are a better predictor of efficacy in cancer animal models than are, of instance, Cmax values consequently the emphasis on maintaining continous exposure in these models. We did this by carried out tumor growth studies in the B16 flank model using osmatic minipumps to achieve continuous delivery ABT-518.

Those pumps were implanted on Day 7 and produced the tumor growth curves shown here resulting in a linear relationship between efficacy and exposure up the dose that clogged the pumps. This translates into the need to maintain continuous exposure to 370 ng/mL of ABT-518 in mouse blood to produce 50% inhibition of tumor growth in this model and represents at least one measure of a target concentration for ABT-518.

Identical studies with marimastat and prinomastat have been conducted and gave efficacious concentrations of 130 ng/mL and 20 ng/mL respectively. These values will come up again when compare results from clinical trials.



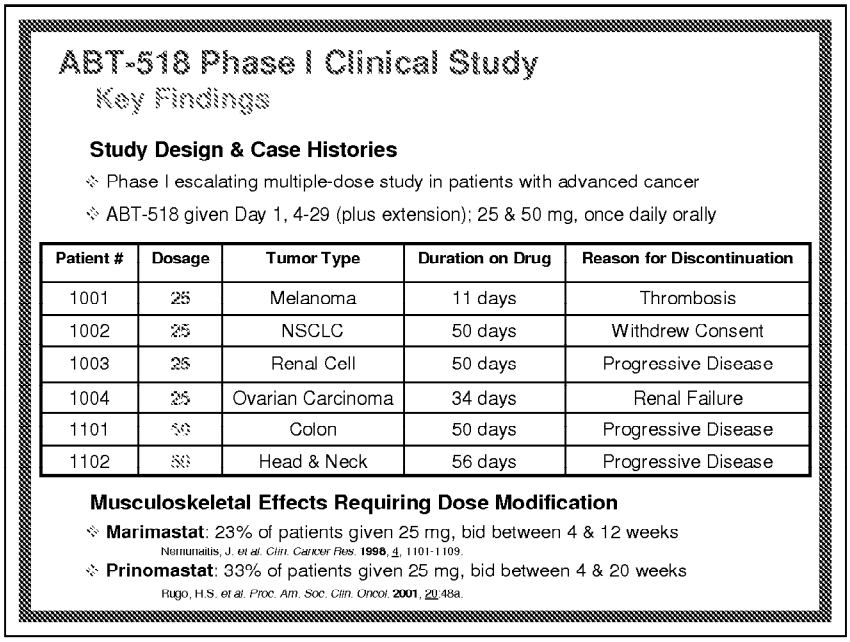
To support the clinical investigation of ABT-518 we have carried out a number of toxicity & safety studies. As you know, the compound is non-mutagenic and non-clastogenic and passed all the CV & CNS safety hurtles.

In multiple-dose toxicity studies, ABT-518 was well tolerated in monkeys given 100 mg/kg once daily for 4-weeks. In rats given 100 mg/kg over the same period we see growth plate changes and increased liver weights. Whether these constitute toxic effects is debatable, yet it is clear that we saw no observable changes in the 10 mg/kg dosing group.

What I show here are the AUCs produced by the No Toxic Effect Dose of ABT-518 in those rat and monkey studies. Those are compared to the predicted AUCs of various doses of ABT-518 in humans based on allometric scaling.

As you can see, the predicted AUCs for doses of ABT-518 up to 400 mg once daily are lower than the AUCs produced by the NTED in rat or the NTED in monkey.

That gave us the safety margin necessary to initiate a Phase I study of ABT-518 in advanced cancer patients which was commenced in March of last year, the design of which is shown here…



ABT-518 Phase I Clinical Study

Key Findings

Study Design & Case Histories

- Phase I escalating multiple-dose study in patients with advanced cancer
- ABT-518 given Day 1, 4-29 (plus extension); 25 & 50 mg, once daily orally

Patient #	Dosage	Tumor Type	Duration on Drug	Reason for Discontinuation
1001	25	Melanoma	11 days	Thrombosis
1002	25	NSCLC	50 days	Withdrew Consent
1003	25	Renal Cell	50 days	Progressive Disease
1004	25	Ovarian Carcinoma	34 days	Renal Failure
1101	50	Colon	50 days	Progressive Disease
1102	50	Head & Neck	56 days	Progressive Disease

Musculoskeletal Effects Requiring Dose Modification

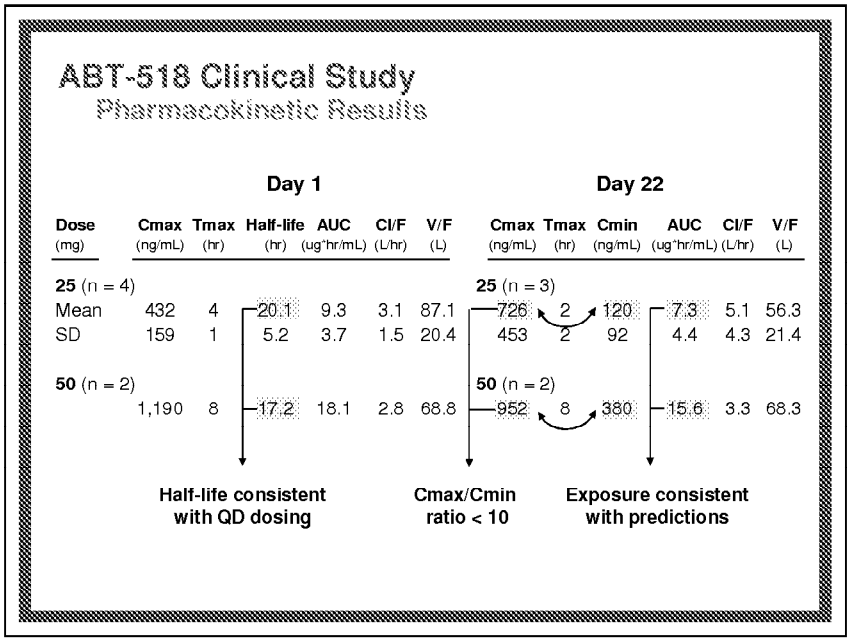
- **Marimastat**: 23% of patients given 25 mg, bid between 4 & 12 weeks
  Nemunaitis, J. *et al. Clin. Cancer Res.* **1998**, 4, 1101-1109.
- **Prinomastat**: 33% of patients given 25 mg, bid between 4 & 20 weeks
  Rugo, H.S. *et al. Proc. Am. Soc. Clin. Oncol.* **2001**, 20 48a.

This study was a multiple-dose Phase I study in patients with advanced cancer. ABT-518 was given orally once daily over one month with extension to longer periods depending on safety and disease progression.

Key Finding are shown here. We had 4 patients on the 25 mg dose for various lengths of time and two patients on the 50 mg dose for 2 months each. The compound is generally well tolerated among these patients. There was one patient with a history of thrombosis who was taken off her anti-coagulant prior to the study who suffered a thrombolytic event. This was deemed not drug related. Another 25 mg patient had undergone a nephrectomy prior to the study and suffered from elevated creatinine levels 4 weeks into the study. Whether is event was drug related has not been determined.

Significantly, what we didn't see in any of these patients is evidence of myalgia and arthralgia akin to what is seen with marimastat. One issue relates to whether we would expect to see joint effects given the number of patients and duration on drug. For comparison, the incidence of joint effects for marimastat and prinomastat are shown here. Now the incidence depends on whether you count all musculoskeletal effects or just those severe enough to cause dose modifications. If you look at just those more severe cases, for marimastat, 23% of patients require dose modifications after being given a 25 mg dose twice daily between 4 and 12 weeks. For prinomastat, 33% of patients given a 25 mg dose require holidays between 4 – 20 weeks.

So the fact that we did not see joint effects in these patients, while not definitive, is certainly encouraging. Obviously another factor that influences whether one is likely to see joint effects relates to ABT-518 exposure which is shown in the next slide.



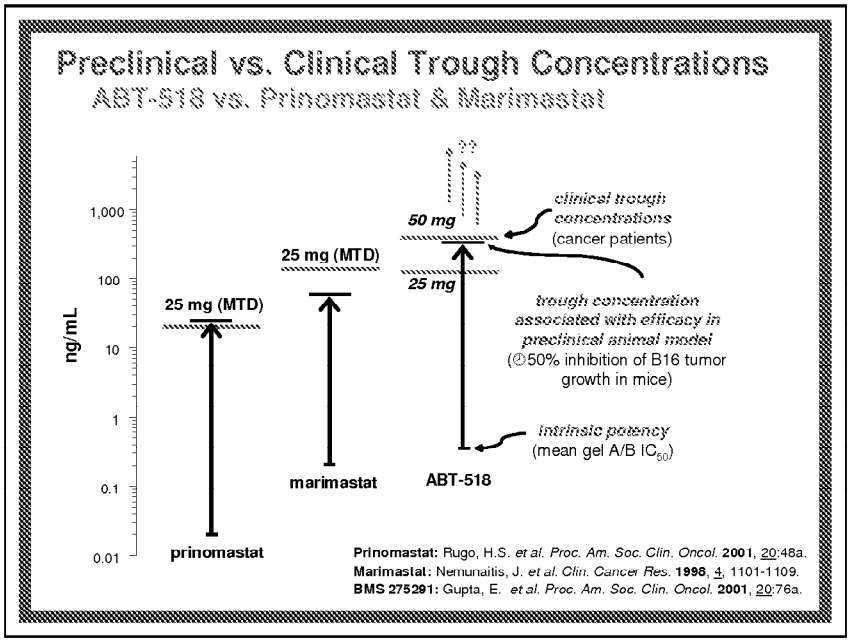
What I show here is pharmacokinetics data on the patients given 25 mg dose of ABT-518 and 50 mg dose at Day 1 and Day 22 of the study.

From both doses we see a half-life consistent with once daily oral dosing (20 & 17 hours) – this was also what was observed in dogs and non-human primates.

One of the ramifications of this extended half-life is a fairly small Cmax to Cmin ratio – here in both cases less than 10 fold. That is certainly different than prinomastat which has been shown to produce a Cmax to Cmin ratio between 30 and 50 fold in cancer patients.

If it turns out that trough concentrations correlate with MMP inhibitor efficacy and Cmax correlate with side effects like joint tox, than a diminished Cmax/Cmin ratio is precisely what one wants in an MMP inhibitor and provides ABT-518 with a clear distinguishing feature vs. the other compounds.

Finally I should point out that the mean AUCs produced by the 25 & 50 mg doses are quite close to the predicted values of 4 ughr/mL and 8 ughr/mL respectively.



Given this pharmacokinetic data and the preclinical efficacy data that I spoke about earlier, one can then being to rationalize why we think prinomastat and marimastat failed in clinical studies and why ABT-518 may not that's shown on this slide.

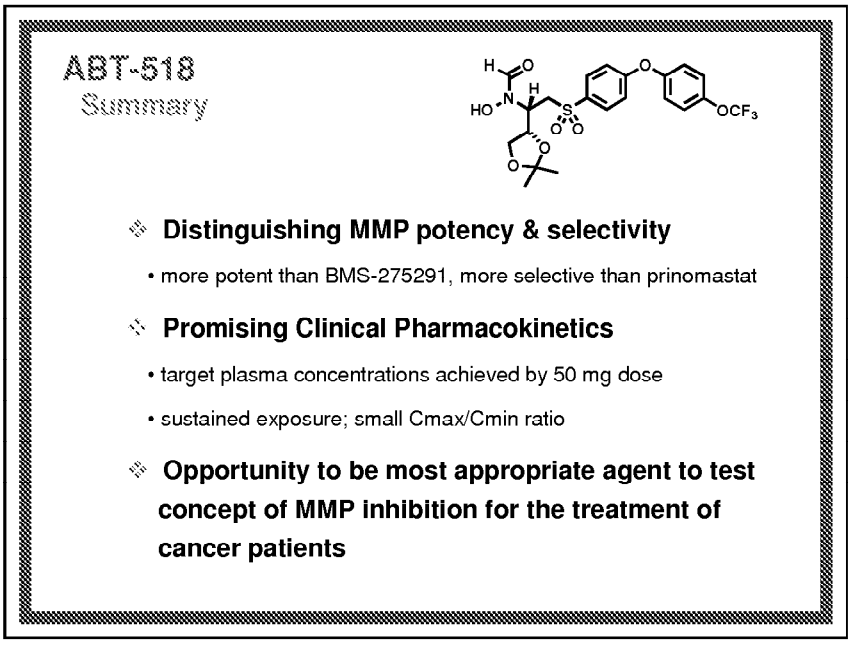
What I show here is the intrinsic potency of prinomastat versus the gelatinases relative to the blood concentration necessary to produce 50% inhibition in the B16 tumor growth model dosed as a continuous infusion… this black bar. I also show the mean trough concentration produced by a 25 mg dose of prinomastat in cancer patients… and that is shown by this red bar. The 25 mg dose of prinomastat is its MTD due to joint effects so this red bar represents a ceiling for the exposure of the drug. Clearly one would want to have the red bar be significantly higher than the black bar to have confidence of efficacy in cancer patients.

A similar shift is seen between marimastat's instrinsic potency and the conc. necessary for preclinical efficacy. The mean trough concentration produced by a 25 mg dose is shown here in red. The red bar is slightly higher than the black bar in this case, however it's important to recognize that dosing holiday's due to joint toxicity are still necessary even for patients on a 10 mg dose of marimastat.

Finally for ABT-518, we see a similar shift from intrinsic to preclinical efficacious conc. for ABT-518. The mean trough concentrations produced by the 25 and 50 mg doses of ABT-518 in cancer patients is shown by the green bars. What we're excited about is that we have achieved plasma conc. in the vicinity of those necessary for preclinical efficacy at the 50 mg dose. Again, while we haven't seen joint effects with either of these doses, the key issue here is how far up we can push this green bar with higher doses of ABT-518. If we can, I think ABT-518 is a better tool to assess the potential benefit of MMP inhibition in cancer patients than marimastat or prinomastat.

I must remind you of several caveots associated with this analysis. First our blood conc. associated with preclinical efficacy is based on a single model – one would ideally like to expand this to a number of tumor models. Second, comparing across species raises the issue of differences in protein binding and, in fact, ABT-518 is more highly protein bound in human plasma compared to mouse plasma. The extent to which this drives this black bar higher is not known. Finally, our clinical data is obviously based on a limited number of patients.

You may have notice that we haven't discussed the BMS compound in this analysis and that's because we haven't run preclinical efficacy studies with BMS 275291. Based on the lack of joint effects of the BMS compound in clinical studies, one would think that it could achieve a large separation between preclinical efficacy and mean trough concentrations. However, for those of you at the SF ASCO meeting you will have noticed that the exposure of BMS 275291 in cancer patients decreases in going from the 1,800 mg dose to the 2,400 mg dose. That was reported in this poster. Consequently, the BMS compound may have reached a ceiling of exposure, albeit for reasons different than with prinomastat and marimastat.

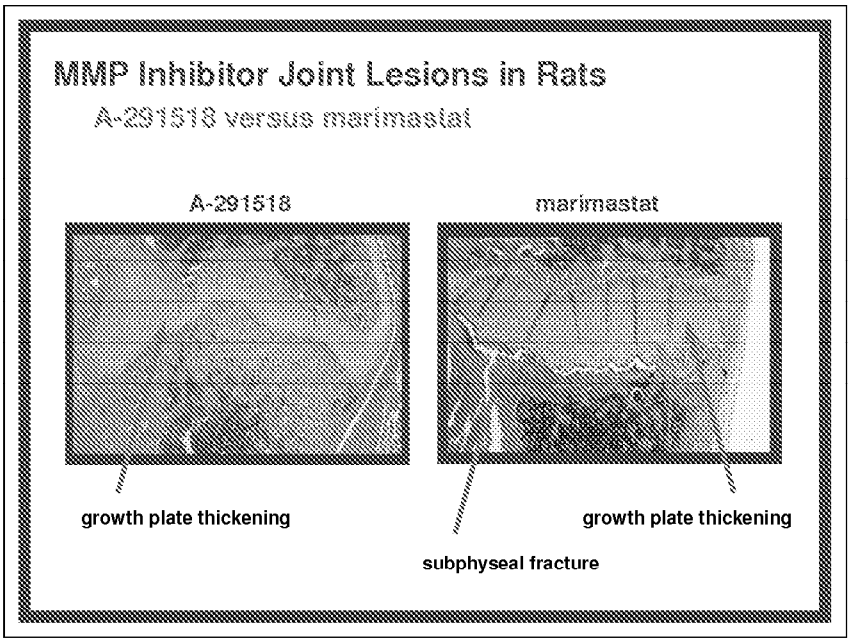


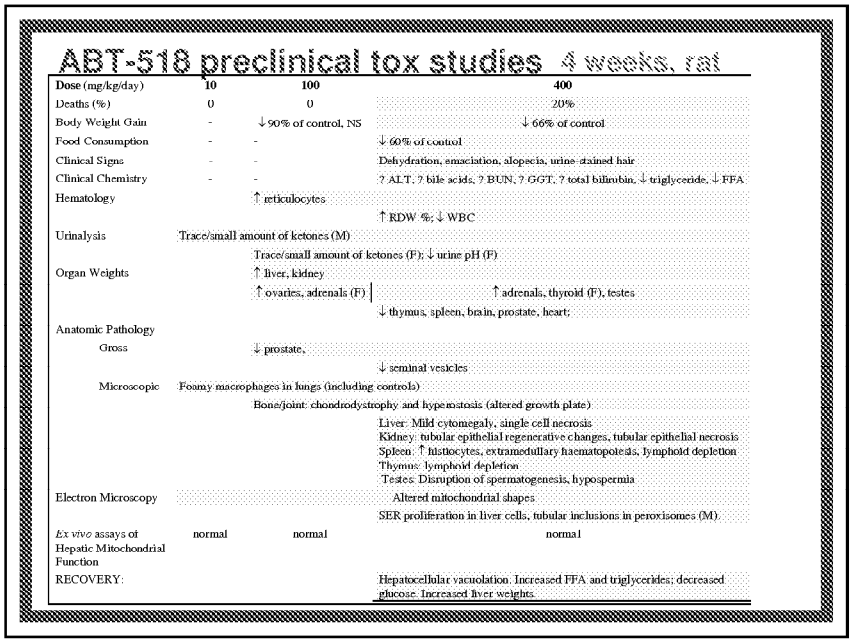
To summarize,

1. ABT-518 displays in vitro potency and selectivity that distinguishes it from other clinical MMP inhibitors.

2. It's clinical pharmacokinetics is also a distinguishing characteristic given its long half-life and small Cmax/Cmin ratio

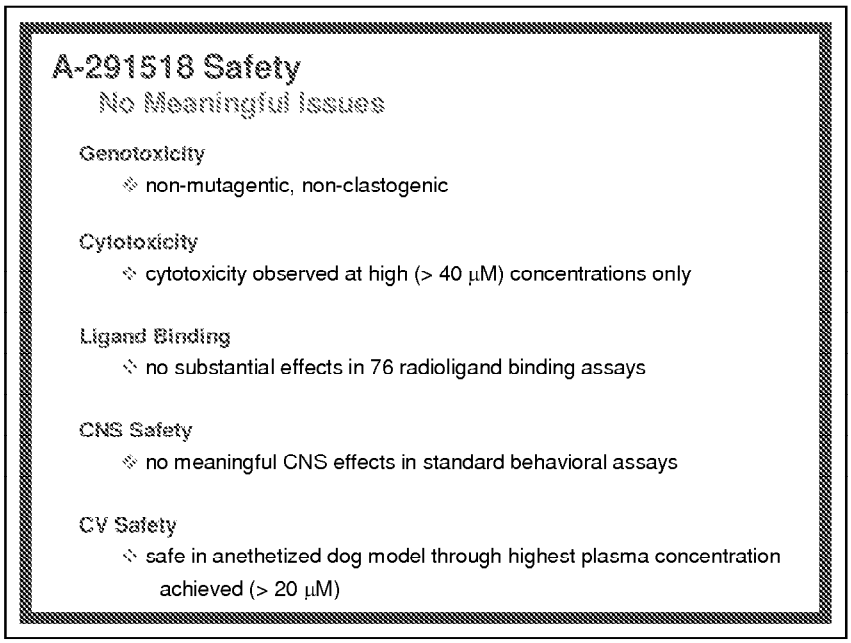
3. The lack of joint effects seen so far to suggest that we may be able to achieve sustained plasma concentrations substantially exceeding those associated with efficacy in tumor models. As a results, we feel ABT-518 has the opportunity to be the most appropriate agent to test the concept of MMP inhibition for the treatment of cancer patients.





ABT-518 preclinical tox studies 4 weeks, rat

Dose (mg/kg/day)	**10**	**100**	**400**
Deaths (%)	0	0	20%
Body Weight Gain	-	↓90% of control, NS	↓66% of control
Food Consumption	-	-	↓60% of control
Clinical Signs	-	-	Dehydration, emaciation, alopecia, urine-stained hair
Clinical Chemistry	-	-	? ALT, ? bile acids, ? BUN, ? GGT, ? total bilirubin, ↓ triglyceride, ↓ FFA
Hematology		↑ reticulocytes	
			↑ RDW %; ↓ WBC
Urinalysis	Trace/small amount of ketones (M)		
		Trace/small amount of ketones (F); ↓ urine pH (F)	
Organ Weights		↑ liver, kidney	
		↑ ovaries, adrenals (F)	↑ adrenals, thyroid (F), testes
			↓ thymus, spleen, brain, prostate, heart;
Anatomic Pathology			
Gross		↓ prostate,	
			↓ seminal vesicles
Microscopic	Foamy macrophages in lungs (including controls)		
		Bone/joint: chondrodystrophy and hyperostosis (altered growth plate)	
			Liver: Mild cytomegaly, single cell necrosis Kidney: tubular epithelial regenerative changes, tubular epithelial necrosis Spleen: ↑ histiocytes, extramedullary haematopoiesis, lymphoid depletion Thymus: lymphoid depletion Testes: Disruption of spermatogenesis, hypospermia
Electron Microscopy			Altered mitochondrial shapes
			SER proliferation in liver cells, tubular inclusions in peroxisomes (M).
Ex vivo assays of Hepatic Mitochondrial Function	normal	normal	normal
RECOVERY:			Hepatocellular vacuolation. Increased FFA and triglycerides; decreased glucose. Increased liver weights.



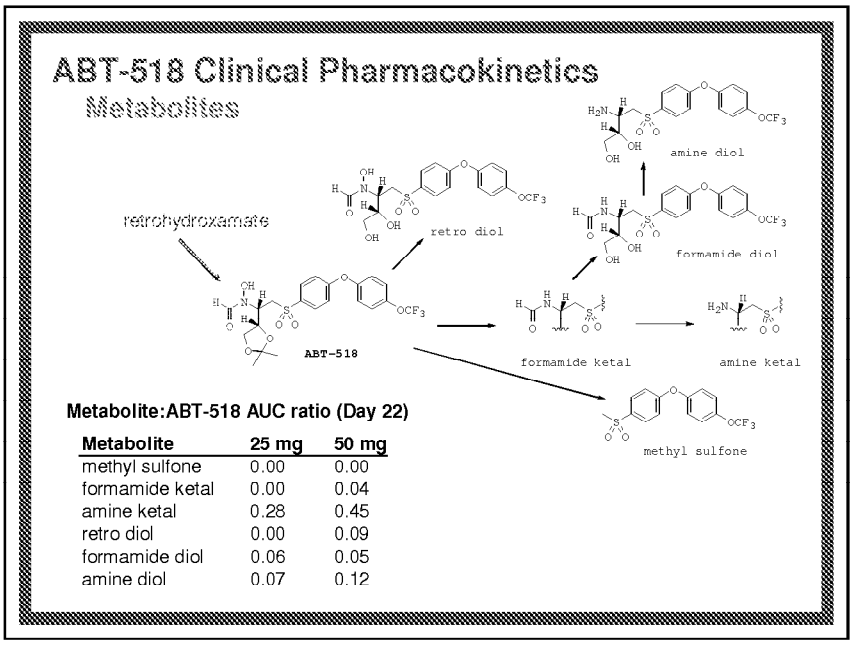
Before we go on to the toxicity studies, a couple of, fortunately brief, words about safety…..

A-291518 non-mutagenic and non-clastogenic

Cytotoxicity is observed only at high concentrations

It has no meaningful effect in a battery of 76 binding assays and no meaningful effects in standard CNS behavior assays.

And the compound is safe in an anethetized dog model of CV safety through the highest plasma concentration achieved which was in excess of 20uM.



We have studied the metabolism of ABT-770 both in vitro and using 13C-labeled material in rats and have constructed the following metabolite pathway.

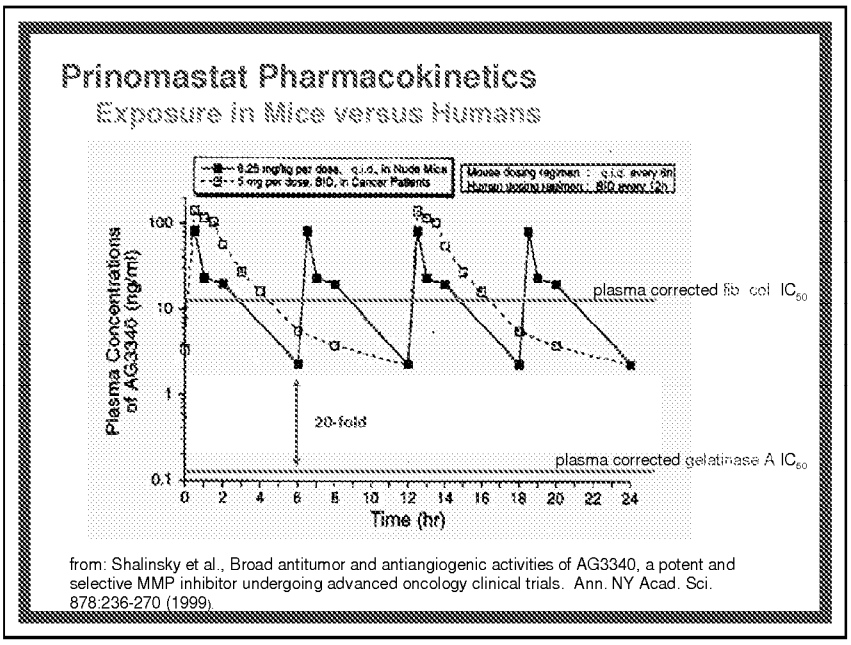
Bile duct cannulation studies suggest that the metabolitc degradation of ABT-770 is initiated by biliary elimination of its glucuronide.

Once in the gut the N-O bond of ABT-770 is reduced giving the fomramide. This is likely mediated by intestinal bacteria since incubation of ABT-770 with rat intestinal contents under anerobic conditions gives rise to the formamide. The formamide is converted to the amine by liver microsomes.

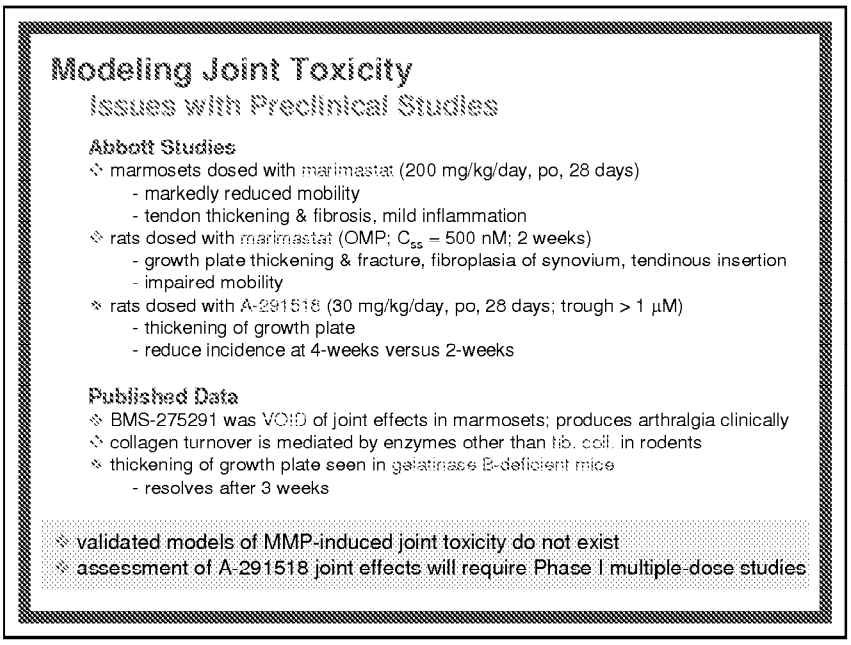
The same deformalyation initiates another pathway which ultimately produces the alcohol via the mixture of oximes shown here.

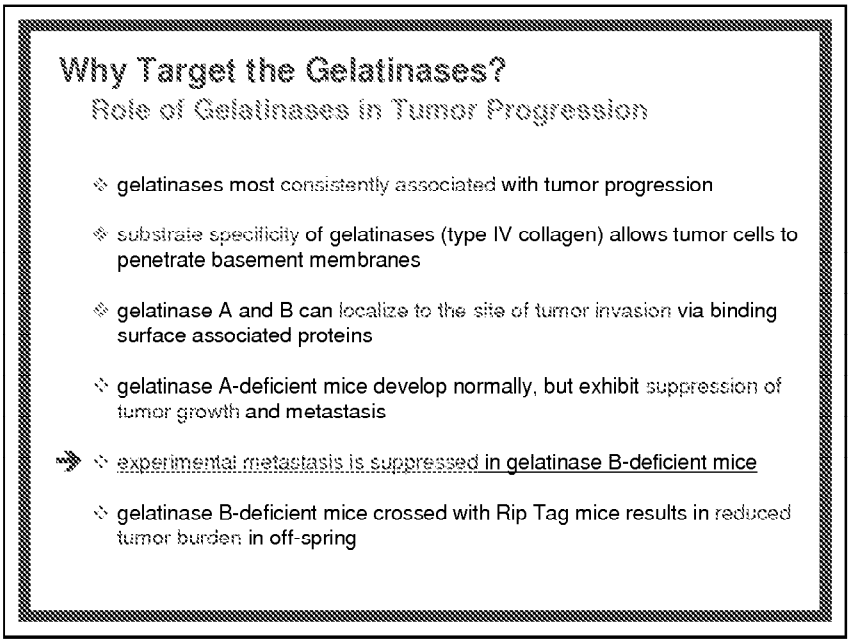
Important to recognize that all metabolites are produced by transformation of retrohydroxamate moiety which chelates zinc at active site of MMPs so none possess MMPI inhibitory activity.

This is for ABT-770, what about the backups?



some MMPs more important than others…. therefore which to inhibit and which to spare?





First, relative to other MMPs, the gelatinases are most consistently associated with tumor progression based on biopsies from a # of different tumor types.

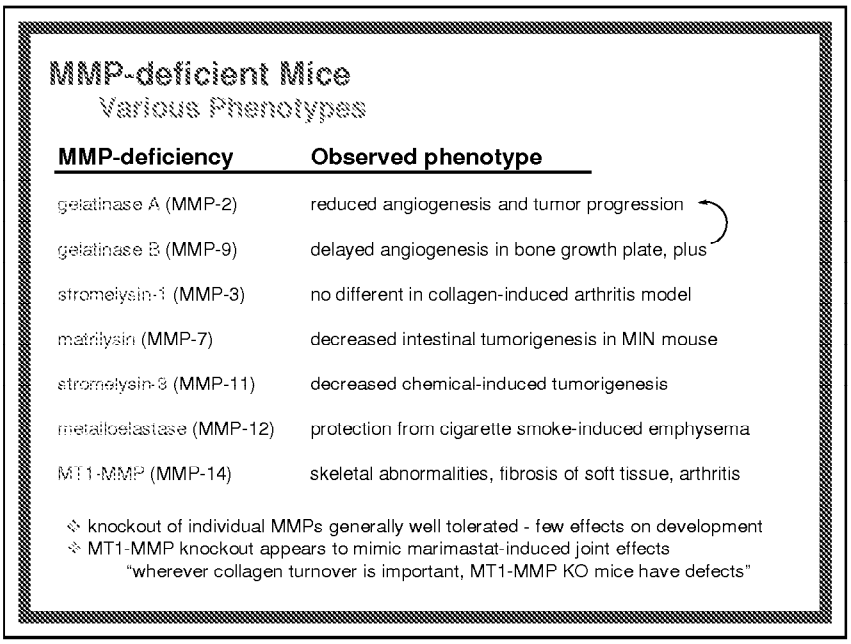
in order for tumor cells to enter vasculature, must degrade basement membranes. Type IV col. is major componenet of base. mem. and good substrate for the gels.

Gel A&B have unique ability to localize to leading egde of invading tumor cells by binding surface associated proteins….

Tumor cells implanted in gel A KO mice grow more slowly and metastasize less readily than normals….

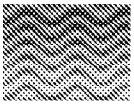
Finally, when gel B KO mice are crossed with a stain of mice predisposed to forming pancreatic cancinomas, see a significant reduction of tumor burden in off-spring.

Based on this evidence, we'd like our compounds to inhibit the gelatinases…. BUT we'd also like to avoid broad MMP inhibition and the reason for that relates to the side effect profile of broad spectrum inhibitors currently in clincal trials...



some MMPs more important than others…. therefore which to inhibit and which to spare?

D's Ex ES



Jane A Hoff-Velk/LAKE/PPRD/ABBOTT

09/24/2003 08:53 AM

To: Raymond A Knight/LAKE/PPRD/ABBOTT@ABBOTT, Susan M Glad/LAKE/PPRD/ABBOTT@ABBOTT, Robert Hansen/LAKE/PPRD/ABBOTT@ABBOTT, Robert A Carr/LAKE/PPRD/ABBOTT@ABBOTT

cc:

bcc:

Subject: Re: ABT-518

I am in the process of sending ABT-518 out again to a prospective licensee. I have already sent the DDC package, but they are inquiring about clinical data and I recalled that this compound was in the clinic. I found this e-mail series in my files and I want to ask if the attached IB below was the most current such that I can send it out and also can I get a copy of the final approved PK summary that was being put together back then. I think Ray may have sent me a copy of the report prior to its approval, but told me I could not send it out, so I may have eventually deleted it. Please advise. Thank you for your help.
Jane

P.S. I am also sending ABT-100 out, and I just want to verify that no clinical studies were even started on that one.

Jane A. Hoff-Velk, Ph.D.
Senior Manager, Scientific Assessment - Oncology
Licensing and New Business Development
Global Pharmaceutical Research & Development
Abbott Laboratories
200 Abbott Park Rd. AP34-2, DR50H
Abbott Park, IL 60064-6187
847-938-5478 phone
847-938-5290 fax
Jane.Hoff-Velk@abbott.com

----- Forwarded by Jane A Hoff-Velk/LAKE/PPRD/ABBOTT on 09/24/2003 08:50 AM -----

Kurt Wehrle

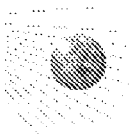
01/15/2002 08:49 AM

To: Jane A Hoff-Velk/LAKE/PPRD/ABBOTT@ABBOTT

cc:

Subject: Re: ABT-518

FYI
----- Forwarded by Kurt Wehrle/LAKE/GPRD/ABBOTT on 01/15/2002 08:50 AM -----



Steven K Davidsen

01/08/2002 03:01 PM

To: Susan M Glad/LAKE/PPRD/ABBOTT@ABBOTT, Robert A Carr/LAKE/PPRD/ABBOTT@ABBOTT, Robert Hansen/LAKE/PPRD/ABBOTT@ABBOTT, Azmi A Nabulsi/LAKE/PPRD/ABBOTT@ABBOTT, Kurt Wehrle/LAKE/GPRD/ABBOTT@ABBOTT

cc:

Subject: Re: ABT-518

No problem with your timetable, Sue. My interest in having the results sooner relates to our interaction with Salmedix. It seems to me that we ought to have all our data compiled and analyzed before we continue talking with them.

Steve
Susan M Glad

Susan M Glad
01/08/02 01:58 PM

To: Robert A Carr/LAKE/PPRD/ABBOTT@ABBOTT
cc: Raymond A Knight/LAKE/PPRD/ABBOTT@ABBOTT, Steven K Davidsen/LAKE/PPRD/ABBOTT@ABBOTT, Robert Hansen/LAKE/PPRD/ABBOTT@ABBOTT
Subject: ABT-518

Bob:

Here are the 2 documents you requested.

Steve: Bob tells me that he thought he could complete the PK report in 5 weeks (by 2/15). Our own internal schedule does not have us completing the clinical summary until 3/29. Will having a final PK/Clinical summary by 3/29 be any problem for you? If yes, please let me know what your preferred timeline might be so I can see if it is possible .

Sue


M00-235 Amendment 2 2-1-01.d


Microsoft Word - BROABT51811_16Final.

D's Ex ET

ASIA TRIP REPORT (FEB 16-20, 2004) PERRY NISEN

- JAPAN (ABBOTT DEVELOPMENT TEAM, PROFFESSOR SAIJO, FUJISAWA) February 16-17, 2004 (sent previously)
- **SINGAPORE (ECONOMIC DEVELOPMENT BOARD, NATIONAL HELATHLCARE GROUP, BIOPOLIS/GENOME INSTITUTE, HEALTH SCIENCE AUTHORITY, SINGHEALTH) February 18-19, 2004**
- **TAIWAN (NATIONAL HEALTH RESEARCH INSTITUTE, DEPARTMENT OF HEALTH, MINISTRY OF ECONOMIC AFFAIRS) February 20, 2004**

PURPOSE:

1. Follow-up to Jeff Leiden's request following his trip to Singapore in November 2003 that we pursue phase IIa trials using the Singapore Cancer Network .
2. Determine if the Taiwan Cooperative Oncology Group has similar clinical trials capability
3. Explore alternative funding/R&D support mechanisms in both countries to maximize the value of our oncology portfolio

RECOMMENDATION: In Singapore, initiate at least one phase 2 clinical trial at SingHealth, establish collaboration between Ed Liu's Genomics Institute and Abbott on biomarkers, and have our business development team determine if the Economic Development Board (EDB) is an appropriate source of development funds for the Abbott Oncology Portfolio core compounds and/or outlicensing of our non core assets. Continue to explore a similar relationship with Taiwan NHRI (their NIH) and Ministry of Economic Affairs (MOEA), but this is much less likely to occur.

SINGAPORE

There are ~ 4,500 new cancer cases in Singapore; #1 cause of death. Spectrum of cancers is similar to US, with higher rates of gastric cancer (but not that much liver or nasopharyngeal, contrasted to other Asian countries). Most clinical trial experience is phase 2. ~ 7% of patients go on clinical trials. The standard of care is very similar to the US. Most patients are treated at one of two government - sponsored groups (divided geographically) (~10% of patients are seen at a private hospital).

National Healthcare Group (West Singapore)

~20% of patients (John Wong, Director).Overall, rather underwhelming. Although John Wong is very accomplished, he wears many hats, and there appears to be only one other (young) medical oncologist, who was too busy in clinic to see us. They are also affiliated with the National University Medical School and the Johns Hopkins Program (which, to date, has been a failure). I am not convinced they can conduct timely, high quality clinical trials. They are somewhat affiliated with Ed Liu's Genomics program in biomarker discovery and are trying to create their own, internal, fully integrated drug discovery enterprise (HTS, formulation, tox, etc). . They participate in CTRG (a cooperative group including institutions in Singapore, Australia, South Korea and Hong Kong).

SingHealth (Joseph Wee, Director) (East Singapore)
~70% of patients. Gary Gordon and I were impressed by their investigators, facility and existing clinical trials infrastructure.
World-class facility: PET, MRI, film-free radiology, radiation oncology, etc. Strong MDs: surgical oncology, medical oncology, other subspecialties function together as a multidisciplinary tumor board. Standard of care per NCCN guidelines. Good clinical trials infrastructure: statistics (outstanding), clin pharm, pharmacy, data management (uses Oracle Clinical), monitoring, coordinators. Some bench research (not impressive). Affiliating with Duke to establish a graduate school and capabilities for conducting large phase 3 trials (in other therapeutic areas like cardiovascular). They don't seem to get along very well with the National Healthcare Group (but are working on it). They currently have a mixture of investigator IND and sponsored trials (according to them: 4 X ph 1, 46 X ph 2, 59 X ph3, 30 X ph 4), multi- and single institutional trials, including CTRG (cooperative group) studies. They have had great execution on lung and breast cancer studies, and their stated preference is for new phase 2 studies for renal cell, bladder and prostate. There is additional capability for SCLC and GI cancers; unclear about lymphoma. They really want to develop phase 1 capabilities, but have very limited experience with first in man studies to date. There is a central IRB and contract mechanism for the member institutions of SingHealth. It looks like they can get a trials started within three months of protocol (two months would be a stretch goal). I'm enthusiastic that they can do timely, cost effective, high quality phase 2 cancer trials, can participate in phase 3 if we want in the future, and will develop phase 1 expertise over time.

Center for Drug Administration (their FDA)
Knowledgeable, well-organized. They described their 3 paths for approval: full NDA (slow), abridged evaluation process (like an expert report-fast), or verification route (new, seems very fast) based on approval by two or more recognized agencies (US, UK, Canada, EMEA, Australia).

Meeting with EDB (Economic Development Board)
It is clear that durable job creation is the top priority. They want to bring biopharma manufacturing to Singapore (highlighting success of Merck), and Jeff's November 2003 memo identified the initiatives he wanted Sandro and others to work on (Singapore Biologics group, post-doc training, Wyeth nutritional manufacturing capacity, etc) - I explained that manufacturing was outside my scope. They were also highly focused on the creation of pre-clinical drug discovery centers in Singapore, highlighting their recently established Novartis Tropical Medicine Institute (170 people) and leveraging Ed Liu's Genomics Institute in the Biopolis (see below). They were also interested in the creation of an Asian Clinical Trials Center for phase 1, much like what Lilly established (parenthetically, Lilly are very pleased with this unit). Because the EDB venture arm invested in Raven, they inquired aggressively about bringing some of that collaborative disercovery research to Singapore. They have emerging capability in toxicology - building a primate breeding facility on an adjacent island, and

beginning some contract toxicology work. There may also be some capability and capacity for pre-clinical pharmacology (ie disease models using transgenic/ko mice) and the possibility of freedom to operate on HTS of particular targets that may be encumbered in the US.

I indicated that for Abbott Oncology, the focus needs to be on early clinical development and not discovery. That being said, Jerry Wenker is already in discussion with them about licensing two of our deprioritized compounds (not oncology).

In our discussions, they distinguished between priority compounds currently in or about to be in development [atrasentan, ABT-510, ABT-751, ABT-472 (PARP), ABT-869 (multi targeted kinase inhibitor), ABT-007 (epo mimetic-was not discussed)] and non-priority compounds (ie programs that are currently on pause or killed for prioritization reasons) [ABT-828 (K5), ABT-100 (FTI), ABT-518 (MMPI), ABT-963 (Cox-2)]. I indicated the need for 1) speed, 2) lower cost, 3) high quality, and 4) managing risk/maximizing portfolio value through determining strong, early signals of activity. I indicated that it might be possible to consider outlicensing of the 'non-priority' compounds (already in discussion for two non-oncology assets) +/- opportunity to license back after proof-of-principle, and also investment in the oncology portfolio in exchange for royalties and/or geographic commercial rights, but that these discussions were the purview of Jim Tyree and our Business Development Office.

In general terms, they proposed two different types of models:
Model 1. Abbott Oncology Research in Singapore. Create a structure that complements our existing Global Oncology R & D Effort. Concentrate on A) Pre-clinical 'Experimental Medicine': HTS, toxicology, pre-clinical pharmacology (animal models) and B) Clinical Development: Clinical trials, coordination and management of studies, data management, protocol development, manpower training, etc. They suggested that an Abbott Singapore R & D Center could be supported in part from EDB with up to 50% R & D grants supporting manpower, consumables, equipment, IPR for preclinical work and grants for start-up manpower training for clinical development. This R & D center could leverage collaboration with Singapore strategic partners: Genome Institute, National Cancer Center, CTRG, and Singapore Cancer Syndicate.
Model 2. Leverage Singapore Drug Development Vehicle (DDV) for Non-Priority Candidates and Indications. Out license compounds deemed non-core with in-license buy back/commercialization rights. The DDV could add value to assets by progressing them from late preclinical through phase 2, focusing on oncology and antiviral. They could outsource clinical development work and trials to CROs, CMO if needed and contract labs.
These models are highlighted in some slides that they put together after our meeting and will be sent under separate cover by regular mail.

Biopolis/Genomics Institute
Ed Liu set up an impressive institute with unique capabilities focusing on expression profiling, SNP analysis, genome sequencing (they did SARS virus), some proteomics, some CGH. They are quite involved in cancer biomarker development and have a good historic relationship with Steve Seelig and Vysis. I will follow-up and make connections between them, Steve Fesik and Discovery and also the Global Project Teams to see if there are specific places we can work together.

Next steps

1. Establish connections between Abbott (Fesik, Global Project Development Teams and Seelig (Vysis)) and Ed Liu (Singapore Genomics Institute) to see if there is a way to collaborate on one or two specific biomarker projects in discovery and early development (Nisen)
2. Make a connection between SingHealth and AACR/ASCO to use Singapore as the Asian site for clinical trials course currently taught annually in US and Europe by Dan Von Hoff et al. (Nisen)
3. Abbott to send full dossiers on our entire portfolio under CDA, including compounds on not currently funded: ABT-100, ABT-518, ABT-828, ABT-963, also ABT-22, 869, 510, 751 and 627. (Wei-Chi Liao)
4. SingHealth will send us summaries of their CRO audit reports
5. Find out if the Commonwealth Foundation (or other source) will fund research nurses and MD time (this is the bottleneck in being able to conduct more clinical trials- otherwise they have the capacity to do many more studies. Singhealth will determine the actual cost of hiring additional research nurses and an MD.
6. SingHealth to determine the possibility of conducting neoadjuvant studies in HNSCC/NPC, HCC, breast, prostate, rectal, gastric or skin cancer.
7. Abbott will prioritize the ph2 studies we would most like them to conduct based on their capacity and interest (Gordon)
8. Abbott Business Development to investigate further if, through the EDG, they want to license any of our non core assets and/or invest in our entire oncology portfolio (Jerry Wenker to define the extent of investment and what types of return would be possible- eg royalties, Geographic commercial rights, etc)
9. Ask Immunoscience about their interest in conducting a cancer cachexia/fatigue study with Humira – there is specific academic palliative care experience in Singapore (Nisen)
10. Explore the possibility of Singapore as beta site for remote data entry of phase 2 clinical trial data interfacing with Oracle Clinical (the database they use and which we are moving over to) (Gordon)

TAIWAN
There are > 50,000 new cancer cases annually. 90% of patients are seen at hospitals affiliated with the NHRI (their NIH). Most institutions use a common IRB and central contract management. In contrast to Singapore, the standard of care is lower and neither facilities nor investigators are as sophisticated. Overall, there is less clinical trial expertise.

National Health Research Institute (NHRI)
There are over 20 affiliated hospitals. Dr. Jackie Whang-Peng, who directs the Division of Cancer Research, was previously at the NCI for many years. The associate director (Dr Chien) spent 20 years at Merck in cardiovascular discovery. There is decent bench research, and they are developing clinical trial expertise. Paul Carbone helped them establish the Taiwan Cooperative Oncology Group, modeled after the ECOG cooperative group in the US. To date, they have mostly done phase 2 studies in hepatocellular and nasopharyngeal carcinoma. They are very enthusiastic and motivated to work with us, but I am not confident that they will be able to conduct speedy, low cost, high quality clinical trials.

Department of Health
We met with the head of their FDA who is very impressive and experienced. She would like to help us find a way to work with the NHRI but she wears two potentially conflicting hats- one as a government official and the other as an advocate for R & D in her country.

Ministry of Economic Affairs
We had a perfunctory meeting with the Vice Minister. Like Singapore, they are focused on job creation. Biopharma is a key area of focus for growth. Other staff summarized the various tax incentives for business and I commented that we were already doing manufacturing in Taiwan (ABT-578 for drug coated stent). 50% matching funds are available for R &D.

<u>We discussed two models for Abbott-Taiwan collaboration</u>:

1. Use the 50% government R & D incentive to decrease the cost of oncology development in Taiwan. This is less appealing because I am not confident there is an adequate clinical trial infrastructure to conduct the studies we want.
2. Create a NewCo offshoot of NHRI with the help of the MOEA to generate capital that will enable them to either license some of our non-core assets (and jump start their Biotech/biopharma with compounds ready for the clinic) and/or invest in the Abbott Oncology portfolio, in exchange for royalties and/or geographic rights. They were thinking about a $ 30 MM investment.

Next steps

1. Abbott to explore the R & D incentive from MOEA to decrease the cost of clinical trials in Taiwan, and further assess their clinical trial capability beyond hepatocellular and nasopharyngeal carcinoma (G Gordon)- the first impression is that this is a no go because of their limited clinical trial expertise
2. Abbott atrasentan global project team to formally review the NHRI atrasentan colorectal cancer trial proposal and to reply directly to Dr. Chien about our willingness to support the study (A Allen) – again, probably a no go for funding reasons and their limited clinical capability
3. NHRI to evaluate creation of a NewCo entity as an investment vehicle to either a) license non core Abbott compounds currently paused in development (ie ABT-100, 518, 963, 828), and/or b) fund clinical trials with compounds currently in development (ie atrasentan, ABT-510, ABT-751) for indications that we are not currently pursuing (eg hepatocellular carcinoma, gastric cancer)
4. Abbott to clarify our rights to ABT-751 for Taiwan (I think Eisai holds them) (G Gordon)
5. Abbott to determine:
    a. How much R & D investment we are looking for to fully develop the Abbott Oncology Portfolio worldwide (P Nisen→J Wenker)
    b. What (if anything) we would be willing to give up for such an investment (J Wenker)
        i. A royalty based on sales that emerge from commercialization which occur as a result of their sponsored study (along the lines of the Goodwin/Commonwealth Foundation deal)
        ii. Limited geographic commercialization rights for some product in exchange for broader investment in the portfolio
6. Sign full CDA and share complete dossiers of our compounds with NHRI (Wei Chi Liao)
7. NHRI to identify business point of contact for discussions with corresponding delegate from Jerry Wenker's organization (if there is a next step)

Meeting with Japan Development Team
Purpose: obtain update on atrasentan trials, present new oncology compounds entering development, and discuss future plans.

1. Update on atrasentan phase 1 trial: 1 patient enrolled, 6 in screening. Discussed strategies to catch up timeline (open another site), and prevent delays for future studies (better communication with GPT, make sure protocols are finalized in Abbott Park before sending them to Japan, insure that eligibility criteria and other details are acceptable to investigators before initiating studies).
2. Learned about competitor molecules under development in Japan : AstraZeneca (ZD4050), selective endothelin A receptor antagonist, phase 2 for prostate cancer ROW; phase 1 healthy volunteers in Japan; they want to conduct study in Japanese prostate cancer patients, but National Cancer Center won't do it until ours is completed. Yamanouchi (YM598), less selective endothelin A receptor antagonist, phase 2 ROW; awaiting our results before they decide on phase 3 and studies in Japan.
3. Reviewed the Abbott Oncology Portfolio and recent DDC approvals (ABT-472 PARP inhibitor, ABT-869 multi targeted kinase inhibitor, ABT-007 erythropoetin mimetic, and discussed overall strategy for developing cancer drugs in Japan. There are two basic approaches: 1) parallel phase 1 in Japan , then inclusion of Japanese cohort in phase 2 studies (this approach enabled early registration in Japan of Iressa), or 2) start phase 1 in Japan after successful phase 1/proof-of-principle in US/EU. This bridging strategy is lower risk but, in general, precludes simultaneous filing, and perpetuates perception of Japanese market opportunity as secondary to US/EU.

My overall impression is that Nakamura-san and team are doing a solid job, and that Nakamura-san really understands the oncology marketplace and cancer drug development challenges in Japan; Nakamura-san has a good relationship with Professor Saijo (see below). There seems to be an overall need for more CRAs (the Abbott Program was described as significantly smaller than corresponding teams of other global Pharma companies developing drugs in Japan).

Meeting with Nagahiro Saijo MD, Chairman, Medical Oncology, National Cancer Center

1. Provided update on atrasentan and reviewed the Abbott Oncology portfolio. He seemed enthusiastic, asked insightful questions, and invited us to make a formal presentation to the National Cancer Center (much like has been done recently by Novartis and AstraZeneca). Saijo is the key opinion leader for all oncology clinical trials (and registrations) in Japan. He was pessimistic about being able to develop

ABT-510 thrombospondin mimetic in Japan, as self-injection would be problematic and he didn't think that efficacy was particularly dramatic.

Interviewed Dr. Ito for program manager position.
I would not recommend him for hire. Although his medical training was outstanding, he was very nervous, had difficulty communicating, did not have leadership skills, and would not likely interact effectively with global project teams. His experience at AstraZeneca may have been useful, but it is unclear why he gave up his position there last May (he claims it was a reorganization and that he did not want to perform a medical consulting position)

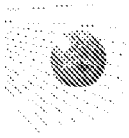
Fujisawa
As a follow-up to a meeting Holger Liepmann and Guillermo Herrera had with Fujisawa, we had an introductory meeting with R & D scientists in Tsukuba. Unfortunately, only the Fujisawa Discovery organization was represented. I presented a non-confidential overview of the Abbott Portfolio. They did not want to discuss their HDAC inhibitor (FK228), which is in phase 2 (I think it is about to be licensed to a small US Biotech). Fujisawa Discovery focus is on transplantation, metabolic disease, urinary dysfunction, Alzheimer's, stroke, and antifungals. Discovery hit to lead work is done in Tskuba then transferred to Osaka. They described an adenosine deaminase inhibitor in or near the clinic that may be useful for hematologic malignancies and possibly immunoscience - they thought there might be interest in some sort of partnership/licensing arrangement.

Actions Items:

1. Holger Liepmann, John Leonard, Eugene Sun and Toshi Kato need to discuss ways to better integrate the Japan Development organization with GPRD and Global Project Teams. Although the four of you may want to discuss it alone, I think Marleen Verlinden, Jim Lefkowith, Chris Ward and I can offer additional perspectives. I will set up a teleconference if you want.
2. Oncology Global Project Teams (Gary Gordon - ABT-472, Andrew Allen – atrasentan and ABT-007, Rod Humerickhouse – ABT-869) will make contact with Toshi to start planning/budgeting for work in 2005.
3. Nakamura-san will arrange with Professor Saijo for Abbott Oncology to make a formal presentation to the National Cancer Center.
4. I will forward a copy of the Japan Development and Regulatory Review presentation to Guillermo Herrera on 2/3/04 to John Leonard, Eugene Sun and Chris Ward.
5. I will ask business development to contact Fujisawa to see if there is interest in potential partnering on the ADA inhibitor (or other development projects of common interest in core areas of immunoscience and neuroscience). If so, we can sign a CDA and evaluate the data.

6. I will update Toshi about the outcome of the March 7 meeting with FDA on atrasentan.
7. I would encourage that additional candidates be interviewed for the project manager position. I think Toshi would agree that Dr. Ito would not be appropriate for the job.

D's Ex EU



Steven K Davidsen /LAKE/PPRD/ABBOTT

05/25/2004 11:31 AM

To: Susan M Glad/LAKE/PPRD/ABBOTT@ABBOTT, Dawn M Carlson/LAKE/PPRD/ABBOTT@ABBOTT, Sindee Sommer/LAKE/PPRD/ABBOTT@ABBOTT

cc:

bcc:

Subject: Re: ABT 518

We talked with several companies/institutions about ABT-518 several years ago with no success. As you may be aware, the MMPI field was deflated by negative clinical results with AG3340 and marimastat. It is therefore safe to say that ABT-518 is on the "inactive" list.

Steve
Susan M Glad

Susan M Glad

05/25/2004 09:48 AM

To: Dawn M Carlson/LAKE/PPRD/ABBOTT@ABBOTT
cc: Sindee Sommer/LAKE/PPRD/ABBOTT@ABBOTT, Steven K Davidsen/LAKE/PPRD/ABBOTT@ABBOTT
Subject: Re: ABT 518

Sindee:

No, there is no patient activity on this compound. The Ph 1 study ended back in 2001 and no further development has been initiated. Abbott may be trying to identify a development partner but I have not heard anything about one having been selected. Steve, do you know the status of 518?

Susan Glad-Anderson
Assistant Director
Abbott Oncology
Dept. R48K, Bldg. AP30-3
Tel: (847) 935-1356 Fax: (847) 937-7812
e-mail: susan.glad@abbott.com
Dawn M Carlson

Dawn M Carlson

05/25/2004 09:40 AM

To: Sindee Sommer/LAKE/PPRD/ABBOTT@ABBOTT
cc: Susan M Glad/LAKE/PPRD/ABBOTT@ABBOTT
Subject: Re: ABT 518

Sindee,

I believe that this compound is no longer being developed. Sue, can you let Sindee know whether it has officially been "killed"?

Dawn M. Carlson, MD, MPH
Medical Director
Angiogenesis Team, Oncology Group
Abbott Laboratories

Phone: (847)938-0618
email: dawn.carlson@abbott.com
Sindee Sommer

Sindee Sommer
05/25/2004 09:25 AM

To: Dawn M Carlson/LAKE/PPRD/ABBOTT@ABBOTT
cc:
Subject: ABT 518

Dawn,
Hi.
Do you know if 518 is still alive and in develpment?
We haven't received any cases from it in a long time and we wanted to know if it had been killed or if it was still active?

Thanks,
Sindee

P's Ex 13

ABBOTT

Daphne L. Pals
Senior Counsel

Abbott Laboratories
100 Abbott Park Road
Abbott Park, Illinois 60064-6049
Telephone: (847) 935-5747
Telecopy: (847) 938-1206

September 20, 2001

John Hancock Life Insurance Company
200 Clarendon Street, T-57
Boston, MA 02117
Attention: Bond & Corporate Finance Group
Fax: 617-572-1628

Re: Research Funding Agreement dated as of March 13, 2001
Termination of MMPI Program and ABT-518

Dear Steve,

This is to advise you that Abbott has refocused its efforts in cancer discovery and, as a result, has made the decision to terminate the MMPI Program, which includes Program Compound ABT-518. There will not be any further funding of ABT-518 or the MMPI Program, except as is required to continue to collect data on already enrolled patients.

Section 4.3(c) of the Agreement is not applicable as the cessation of the development of ABT-518 was not the result of Abbott's acquisition of a Replacement Compound. Abbott will attempt to maximize the commercial value, if any, of ABT-518 as required under Section 4.3(d).

Phil Deemer has attempted to schedule a meeting with you to discuss the termination for the MMPI Program, as well as introduce you to Tom Lyons, our new controller, Global Pharmaceuticals Research and Development. Unfortunately, due to scheduling problems, that meeting has not yet occurred. We look forward to scheduling that meeting soon.

I hope you are doing well.

Sincerely,

Daphne Pals

Daphne Pals
Senior Counsel

cc: John Hancock Life Insurance Company
200 Clarendon Street, T-50
Boston, MA 02117
Attention: Investment Law Division
Fax: 617-572-9268

CONFIDENTIAL

ABBT 0025972

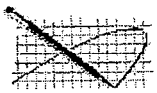
P's Ex AF

Philip M Deemer
03/22/2001 03:34 PM

To: Perry D Nisen/LAKE/PPRD/ABBOTT@ABBOTT
cc:
Subject: Re: Hancock and Alcon

Perry, thank you for your note. I'm sorry about your sister. I don't want to bother you until you get back from things and vacation but perhaps we could sit down then and catch up. I'm off to Hawaii for a break with my dad and Diane. Best regards to you, Amy and family.

Perry D Nisen



Perry D Nisen
03/21/01 10:30 AM

To: Philip M Deemer/LAKE/CORP/ABBOTT@ABBOTT
cc:
Subject: Re: Hancock and Alcon

Phil
Mega mazal tov! You are the most tenacious guy I know- you deserve a new car not just a pen. I know all about the 518 debacle (I tell you more over the phone). Since we killed 839 (this was the FTI) I have no objection to sending them some (talk to Saul). There is much I would like to discuss with you. I'm in LA)(my sister is quite ill), then if she is stable, to Worchester tonight, then Boston, then return Fri night, but out all next week (school break- vacation).
My cell phone is 847 682 7188. I hope you and Diane are well- haven't spoken to you in ages. We need a f/u mtg with Eisai- Azmi has the clinical brochure and protocols- you may want to send those
pn

From: Philip M Deemer on 03/20/2001 09:53 AM

From: Philip M Deemer on 03/20/2001 09:53 AM
To: Perry D Nisen/LAKE/PPRD/ABBOTT@ABBOTT
cc:
Subject: Hancock and Alcon

You probably heard that Hancock was signed last week: $214,000,000 over 4 years! A long time coming but finally done. We had a little scare at the end when it looked like 518 was being slowed down which could have been the deathnell to the deal. I worked with John to protest that and I understand it is back on track.

On another matter, Alcon called me looking for 2g of 839. We don't need to work with them if there is no/little synergy. I told them I thought it would be difficult to give them that amount at this time but that I would check with you.

Perry, We should catch up with one another before too long.

Best regards.